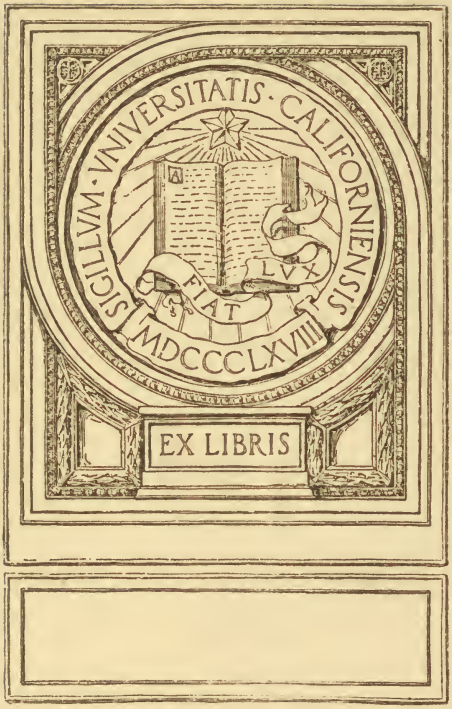
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PHARMACOLOGY AND THERAPEUTICS

FOR

STUDENTS AND PRACTITIONERS OF MEDICINE

BY

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PREFACE

The continued immanence of the U. S. Pharmacopœia has delayed the publication of a new edition of this work, as the author felt that the appearance of a revision which should not include the changes in the legal standard would work an injustice to many of those who should purchase the book. While the general plan of the previous edition has been adhered to, extensive alterations have been required, not only to meet the changes in the Pharmacopœia but also to keep apace with the rapid advances in the sciences of pharmacology. The articles on veronal, digitalis, pituitary, atoxyl and salvarsan have been almost completely rewritten and important alterations made in those on potassium, caffeine, dionine, ergot, ipecacuanha, magnesium, calcium, and hexamethylenamine. Some twenty substances not considered in the previous edition have received more or less extensive notice in the present one; among these may be mentioned especially, agaricin, bromural, apiol, cotarnine, chrysarobin, picrotoxin, homatropine, aspidosperma, and thiosinamin. Besides these there have been a number of minor interpolations scattered throughout the work.

While the author does not feel that he should surrender his judgment as to the importance of various remedies to that of the Committee on Revision, he does believe that official substances should always be favored by the physician when not to the detriment of the patient. Moreover, for obvious reasons, it is important that a text-book for students should recognize the legal authority of the country on the subject of drugs. Therefore, while it has been deemed advisable to consider a number of unofficial drugs, because of their practical importance, it has also been necessary to include some substances of little remedial value because of their recognition by the Pharmacopœia.

One innovation in the U. S. Pharmacopœia which has been followed in this work is especially worthy of note. That is the adoption of the British term "mil" for the thousandth part of a liter. This is a much more convenient as well as a more accurate term than the cumbersome "C.c."

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ABBREVIATIONS

A. A.—Archiv für Augenheilkunde.
A. A. P.—Archiv für Anatomie und Physiologie.
A. C. J.—American Chemical Journal.
A. de P.—Archives de Physiologie normale et pathologique.
A. E. P. P.—Archiv für experimentelle Pathologie und Pharmakologie.
A. G. M.—Archives générales de Médecine.
A. G. P.—Archiv für die gesammte Physiologie des Menschen und der Thiere.
A. Hk.—Archiv der Heilkunde.
A. I. B.—Archives italiennes de Biologie.
A. In. M.—Archives of Internal Medicine.
A. I. Past.—Annales de l'Institut Pasteur.
A. I. P. T.—Archives internationales de Pharmacodynamie et de Therapie.
A. J. M. S.—American Journal of the Medical Sciences.
A. J. P.—American Journal of Physiology.
A. K. C.—Archiv für klinische Chirurgie.
A. M. Ex.—Archives de Médecine expérimentelle et d'Anatomie pathologique.
Amer. Med.—American Medicine.
A. N.—Alienist and Neurologist.
An. d'H.—Annales d'Hygiène.
An. O.—Annals of Ophthalmology.
A. Ph.—Archiv für Anatomie und Physiologie, physiologisches Abteilung.
A. Phar.—Archives de Pharmacodynamie.
Arch. Hyg.—Archiv für Hygiene.
A. R.—Aerztliche Rundschau.
Aus. M. Gaz.—Australian Medical Gazette.
Aus. M. J.—Australian Medical Journal.
A. V. K.—Archiv für Verdauungs-Krankheiten.
A. Z.—Apotheker-Zeitung.
B. A. M.—Bulletin de l'Académie de Médecine de Paris.
B. A. R. B.—Bulletin de l'Académie Royale de Médecine de Belge.
B. G. T.—Bulletin général de Thérapeutique médicale et chirurgicale.
Biochem. J.—Biochemical Journal.
B. K. Ch.—Beiträge zur klinischen Chirurgie.
B. K. W.—Berliner klinische Wochenschrift.
Bull. Med.—Le Bulletin Médicale.
B. M. J.—British Medical Journal.
B. M. S. C. P.—Bulletin et Mémoires de la Société Clinique de Paris.
B. M. S. H.—Bulletin Société Médicale des Hôpitaux des Paris.
B. M. S. J.—Boston Medical and Surgical Journal.
B. P. A.—Beiträge zur Pathologischen Anatomie und zur Allegemeinen Pathologie.
Cb. B.—Centralblatt für Bacteriologie.
Cb. C.—Centralblatt für Chirurgie.
Cb. I. M.—Centralblatt für Innere Medicin.
Cb. N.—Centralblatt für Nervenheilkunde.
Cb. P.—Centralblatt für Physiologie.
Cb. B. S. A.—Correspondenzblatt der Schweizererische Aerzte.
Chi. M. J.—Chicago Medical Journal.
C. K. M.—Centralblatt für klinische Medicin.
C. M. R. V.—Contributions to Medical Research. Vaughn. Ann Arbor. 1903.
C. M. W.—Centralblatt für medicinischen Wissenschaften.
C. R. A. S.—Comptes-rendus de l'Académie de Science, Paris.
C. R. S. B.—Comptes-rendus de la société de Biologie, Paris.
D. A. K. M.—Deutsches Archiv für klinische Medicin.
D. J. M. S.—Dublin Journal of the Medical Sciences.
D. Kl.—Deutsche Klinik.
D. M. W.—Deutsche medicinische Wochenschrift.
D. Z. Ch.—Deutsche Zeitschrift für Chirurgie.
Ed. M. J.—Edinburg Medical Journal.
Fort. M.—Fortschritte der Medicin.
G. A. M. T.—Giornale della Reale Academia di Medicina di Torino.

G. H. M. C.—Gazette Hebdomadaire de Médecine et de Chirurgie.
G. K. H.—Monatsberichte über die gesammtleistungen auf dem Gebeite der Krankheiten des Harn und Sexual-Apparates.
G. M. P.—Gazette Médicale de Paris.
Gl. M. J.—Glasgow Medical Journal.
Guy H. R.—Guy's Hospital Reports.
Hk.—Die Heilkunde.
H. S. Jb.—Hoffmann and Schwalbe's Jahresberichte über die Fortschritte der Anatomie und Physiologie.
Hyg. R.—Hygienisches Rundschau.
I. B. I. M.—Internationale Beiträge zur Inneren Medicin.
In. Dis.—Inaugural Dissertation.
J. A. M. A.—Journal of the American Medical Association.
J. A. P.—Journal of Anatomy and Physiology.
J. Bi. Chem.—Journal of Biological Chemistry.
J. Chem. S.—Journal of the Chemical Society of London.
J. de l'A. P.—Journal de l'Anatomie et Physiologie.
J. de P. P.—Journal de Physiologie et de Path. gen.
J. de Th.—Journal de Thérapeutique.
J. des. Pract.—Journal des Practiciens.
J. Ex. M.—Journal of Experimental Medicine.
J. M. R.—Journal of Medical Research.
J. N. M. D.—Journal of Nervous and Mental Diseases.
J. P.—Journal of Physiology.
J. P. and B.—Journal of Pathology and Bacteriology.
J. P. Ex. T.—Journal of Pharmacology and Experimental Therapeutics.
K. T. W.—Klinische-Therapeutische Wochenschrift.
L. L.—London Lancet.
Lyon M.—Lyon Médicale.
L. M. R.—London Medical Recorder.
M. A.—Merck's Archives.
M. C. C.—Medicinische-Chirurgisches Centralblatt.
M. C. Tr.—Medico-Chirurgical Transactions.
Med. R.—Medical Register.
M. H. H. B.—Marine Hospital Hygienic Laboratory Bulletin.
M. M. W.—Münchener medicinische Wochenschrift.
M. News.—Medical News.
M. N. A. S.—Memoirs of the National Academy of Science.
M. R.—Merck's Report.
M. S. Rep.—Medical and Surgical Reporter.
M. T. G.—Medical Times and Gazette.
M. W.—Medicinische Wochenschrift.
N. Cb.—Neurologisches Centralblatt.
N. O. M. J.—New Orleans Medical Journal.
N. Y. M. J.—New York Medical Journal.
N. Y. M. R.—New York Medical Record.
N. Y. M. T.—New York Medical Times.
O. M. R.—Ohio Medical Recorder.
O. R.—Ophthalmic Record.
Pa. M. S. J.—Pacific Medical and Surgical Journal.
Path. Intern.—Pathologie Interne.
Ph. Post.—Pharmaceutical Post.
P. J. and Tr.—Pharmaceutical Journal and Transactions.
P. M. C. P.—Pester medizinisch Chirurgische Presse.
P. M. J.—Philadelphia Medical Journal.
P. M. T.—Philadelphia Medical Times.
P. P. S. L.—Proceedings of the Physiological Society of London.
Pract.—Practitioner.
Press. M. B.—La Presse Médicale Belgique.
Pr. M. W.—Prager medicinische Wochenschrift.
Prog. M.—Le Progrès Médicale.
P. Tr. R. S. L.—Philosophical Transactions of the Royal Society of London.
R. C.—Revue de Chirurgie.
R. M. S. R.—Revue Médicale de la Suisse Romande.
Rif. M.—La Riforma Medica.
R. T.—Revue de Thérapeutique.
Sb. G. W.—Sitzungsberichte der königliche Gesellschaft der Wissenschaften.
S. Jb.—Schmidt's Jahrbücher der in- und ausländischen gesammten Medicin.
S. M.—La Semaine Médicale.
St. L. C. R.—St. Louis Clinical Record.
St. L. M. S. J.—St. Louis Medical and Surgical Journal.
S. L. P. Y. C.—Studies from the laboratory of Physiological Chemistry of Yale University.
St. P. M. W.—St. Petersburger medicinische Wochenschrift.

T. G.—Therapeutic Gazette.
Ther. Geg.—Die Therapie der Gegenwart.
Th. M.—Therapeutische Monatshefte.
Tr. A. O. S.—Transactions of the American Ophthalmological Society.
Tr. Chem. Soc.—Transactions of the Chemical Society of London.
Tr. I. C. C.—Transactions of the International Congress of Charity, Corrections, and Philanthropy.
Tr. P. C. M. S.—Transactions of the Philadelphia County Medical Society.
Tr. R. S. Ed.—Transactions of the Society of Edinburgh.
T. W.—Therapeutische Wochenschrift.
U. M. M.—University Medical Magazine.
U. N. M. T.—Untersuchungen zur Naturlehre des Menschen und der Thiere. Moleschott.
U. P. L. W.—Untersuchungen aus den Physiologisches Laboratorium zu Würzburg.
U. P. M. B.—University of Pennsylvania Medical Bulletin.
U. S. P.—United States Pharmacopœia.
V. A. P. A.—Virchow's Archiv für pathologische Anatomie und Physiologie.
V. C. M.—Verhandl. des Congresses für Innere Medizin.
W. A. W.—Sitzungsberichte der kaiserlichen Akademie der Wissenschaften zu Wien. Math. Naturwiss. Kl.
W. G. H.—Wochenschrift für die gesammte Heilkunde.
W. K. R.—Wiener klinische Rundschau.
W. K. W.—Wiener klinische Wochenschrift.
W. M. Bl.—Wiener medicinische Blätter.
W. M. P.—Wiener medicinische Presse.
Z. B.—Zeitschrift für Biologie.
Z. C. P. P.—Zeitschrift (Beiträge) zur Chemischen Physiologie und Pathologie.
Z. E. P. T.—Zeitschrift für Experimentelle Pathologie und Therapie.
Z. Hyg.—Zeitschrift für Hygeine und Infectionskrankheit.
Z. F. H. I.—Zeitschrift für Hygiene und Infectionskrankheiten.
Z. K. M.—Zeitschrift für klinische Medicin.
Z. P. C.—Zeitschrift für physiologische Chemie.

PHARMACOLOGY AND THERAPEUTICS

CHAPTER I.

PRELIMINARY CONSIDERATIONS.

DEFINITIONS.

Therapeutics is that branch of the medical art which deals with the treatment of disease, including the use not only of chemical agencies (drugs), but also of various physical agencies and the regulation of the mode of living. The science which treats of drugs is called *pharmacology*. Pharmacology includes *materia medica*, the study of the physical properties of substances used as medicines; *pharmacy*, the science of preparing and combining drugs; and *pharmacodynamics*, the study of the effect of drugs upon the healthy animal organism (physiological action).

In nearly every civilized country there is some recognized list of drugs—setting forth standards for their purity and methods for manufacturing preparations from them—which is known as the *Pharmacopœia*. The United States Pharmacopœia is published by a convention which meets decennially, and is a standard by enactment of the National as well as most of the State legislatures.

Drugs are derived from the animal, mineral, and vegetable kingdom; the greater number of them, however, are of vegetable origin. Vegetable drugs, as a rule, contain some definite chemical substance to which they owe their remedial properties, and which is, therefore, known as the "active principle."

A number of these active principles belong to the class of substances known as alkaloids. An *alkaloid* may be defined as a nitrogenous substance of vegetable origin which is capable of playing the part of an alkali in so far that it forms salts with the acids. As a rule, alkaloids themselves are not freely soluble in water, but the salts which they form are very frequently so; therefore, with one or two exceptions, the alkaloids are usually employed in the form of some salt. Examples: morphine, strychnine, etc.

A *glucoside* is a proximate principle of vegetable origin which can be broken up by mineral acids into a sugar and another radical. Examples: strophanthin, salicin, etc.

Resins are complex bodies uncrystallizable and usually insoluble in water, but freely soluble in alcohol, ether, and chloroform. Strictly speaking, they are not chemical individuals, but more or less intimate mixtures of various substances; many of them have acid properties. Allied to the resins are the so-called oleoresins, which are mixtures of a resin with a volatile oil.

The *volatile oils* represent the active principles especially of many aromatic plants. They have a strong odor, are very slightly soluble in water, but usually soluble in alcohol or ether. They differ from the fixed oils in their greater aroma, but especially in the fact that when evaporated they leave behind no residue, and that they are not saponified by the alkalies. Examples: oil of wintergreen, oil of peppermint, etc.

Many principles of indefinite character have been grouped together under the head of *neutral principles*. They are usually of bitter taste, but differ from alkaloids in that they do not form salts with the acids. Various organic acids may also be the active principles of drugs.

Remedial agents of organic origin usually require more or less pharmaceutical manipulation before they are suited for medical uses. The preparations which are made from drugs are commonly known as *galenicals*, from Galen, the famous Roman physician who lived in the second century. The most important of the official galenicals are as follows:

Preparations Made with a Watery Vehicle.

Decocta.—Decoctions are made by boiling crude drugs for a greater or less time in water.

Infusa.—Infusions are made with water, either hot or cold, without boiling. They are prepared by maceration or by displacement.

Liquores.—Solutions are preparations in which a non-volatile principle is dissolved in water.

Aquæ.—Waters are solutions of volatile principles in water.

Misturæ.—Mixtures are preparations in which one or more medicinal substances are held in suspension in water. Of such nature are *emulsi* (emulsions), in which some oily material is suspended by a gummy or an albuminous body.

Mucilagines.—Mucilages are solutions of gummy substances in water.

Syrupi.—Syrups are sugary liquids, the menstruum or basis of which is water, with in some cases vinegar or alcohol.

Liquid Preparations Made with an Alcoholic Vehicle.

Fluidextracta.—Fluidextracts are fluid preparations so made that one minim represents one grain of the crude drug.

Tincturæ.—Tinctures are alcoholic solutions prepared by maceration, or displacement, from the crude drug, or by dissolving non-

volatile principles. In some of them strong, in others dilute, alcohol is used.

Spiritus.—Spirits are alcoholic solutions of volatile principles, made by direct solution or by distillation from the crude drug.

Vina.—Wines are preparations whose menstruum is wine.

Solid Preparations.

Extracta.—Extracts are solid preparations made in various ways from the crude drug. They are of a consistency suitable for the preparation of pills.

Confectiones.—Confections are medicinal substances beaten up with sugar into a pasty mass.

Trochisci.—Troches, or lozenges, are gummy pellets or disks, so made as to dissolve slowly in the mouth.

Suppositoria.—Suppositories are conical bodies, prepared for introduction into the rectum, where they melt from the heat of the body. Their basis is generally cacao butter or glycerinated gelatin.

Pilulæ.—Pills are small globular masses intended to be swallowed whole.

Unguenta and Cerata.—Ointments and cerates are solid or semi-solid fatty preparations for external use. The cerates, containing wax (cera), are the firmer of the two preparations.

WEIGHTS AND MEASURES.

In ordering drugs we may make use of either the apothecaries'—the so-called English system—of weights and measures or the metric, or French, system. The metric system is universally employed in all civilized lands, except among English-speaking peoples, and is the system officially recognized by the United States Pharmacopœia, but in this country it is rarely employed in actual prescribing. The system of apothecaries' weights and measures used in the United States is as follows:

APOTHECARIES' WEIGHT—APOTHECARIES' MEASURE.

(*Formerly Official in the United States Pharmacopœia.*)

Pound	℔ = 12 Ounces.	Gallon	C = 8 Pints.
Ounce	℥ = 8 Drachms.	Pint	O = 16 Fluidounces.
Drachm	ʒ = 3 Scruples.	Fluidounce	f℥ = 8 Fluidrachms.
Scruple	℈ = 20 Grains.	Fluidrachm	f ʒ = 60 Minims.
Grain	gr. = 1 Grain.	Minim	♏ = 1 Minim.

One of the disadvantages of the apothecaries' system of the weights and measures is the lack of unity between them. While for practical purposes we may regard a minim as a grain, it must be remembered that, speaking exactly, a minim of distilled water weighs but 0.947 grain, and the fluidounce containing 480 minims therefore weighs but 454.61 grains.

In the French or metric system, which has now been adopted throughout nearly the whole of Europe, there is an absolute relation not only between the weights and measures but also between these and the unit of length. In this system the unit of length is the *meter,* which is equivalent to 39.37 inches. The measure of volume is the *liter,* which is the amount which will be contained in a cubical vessel each of whose sides is 0.1 of a meter; in other words, the liter equals one cubic decimeter. It is equivalent to 2.113 pints. The unit of weight is known as a *gramme,* and is the weight of 0.001 liter of distilled water at a temperature of 4° C. Since one cubic centimeter is the same volume as one milliliter, it is evident that one cubic centimeter of water will weigh one gramme.

The whole metric system is based upon multiples of ten, for measures of weights and capacity as well as length. The following table gives the names of the various weights and measures in the French system. It should be remarked, however, that comparatively few of these names are in common use; weights between one gramme and one milligramme are always written as fractions of a gramme rather than a number of decigrammes or centigrammes; the term mil was adopted by the U. S. P. IX instead of the less euphonious C.c. (cubic centimeter) as indicative of a milliliter.

METRIC WEIGHTS.

One myriagramme	Mg.	=	10,000 grammes.
One kilogramme	Kg.	=	1,000 grammes.
One hectogramme	Hg.	=	100 grammes.
One dekagramme	Dg.	=	10 grammes.
One *gramme*	gm.	=	Weight of 1 cubic centimeter of water.
One decigramme	dgm.	=	0.1 gramme.
One centigramme	cgm.	=	0.01 gramme.
One milligramme	mgm.	=	0.001 gramme.

METRIC MEASURES.

One myrialiter	Ml.	=	10,000 liters.
One kiloliter	Kl.	=	1,000 liters.
One hectoliter	Hl.	=	100 liters.
One decaliter	Dl.	=	10 liters.
One *liter*	l.	=	1 cubic decimeter or 1000 cubic centimeters.
One deciliter	dl.	=	0.1 liter.
One centiliter	cl.	=	0.01 liter.
One milliliter..(mil or C.c.)		=	0.001 liter.

Relation of Metric Weights to Apothecaries.—A gramme weighs 15.434 grains. For practical purposes of dosage, however, we may consider a gramme as weighing 15 grains. Two tables are appended, one of approximate relations between the French and English systems, suitable for calculating doses and which affords the basis for the doses used in this book, and one which represents the popular equivalents.

APPROXIMATE EQUIVALENTS OF APOTHECARIES' AND METRIC SYSTEMS.

Grains or minims		Grammes or C.c.	
1/60	grain (or minim)	= 1	milligramme.
1	grain (or minim)	= 0.06	gramme (or mil)
5	grains (or minims)	= 0.3	gramme (or mil)
8	grains (or minims)	= 0.5	gramme (or mil)
15	grains (or minims)	= 1	gramme (or mil)
1	drachm (or fluidrachm)	= 4	grammes (or mils)
2½	drachms (or fluidrachms)	= 10	grammes (or mils)
1	ounce (or fluidounce)	= 30	grammes (or mils)

In prescribing medicine, we usually order it, for convenience, in household measures. Much might be said about the inexactness of this method, but as desirable as it would be to have our patients use accurate graduates, recourse to common household measures is often inevitable; but one point requires emphasis, as it is frequently overlooked by physicians, and that is that a minim is not a drop. Under certain conditions it is possible to drop distilled water so that each drop will measure one minim, but of alcoholic fluids the drop does not measure much over one-half a minim. Speaking generally of the vegetable tinctures, we may allow from 120 to 130 minims to the drachm.

The approximate equivalents of household measures are as follows:

2 drops	= 1 minim (of alcoholic preparations).	
1 teaspoonful	= 1 fluidrachm	= 4 mils
1 dessertspoonful	= 2 drachms	= 8 mils
1 tablespoonful	= 4 drachms	= 15 mils
1 wineglassful	= 2 fluidounces	= 60 mils
1 tumblerful	= 8 fluidounces	= 250 mils

PRESCRIPTION WRITING.

A prescription is an order to an apothecary to dispense medicine. The fallacy of the idea which is prevalent, especially among students, that a prescription is not complete unless it includes a number of ingredients cannot be too strongly emphasized. A properly written order is a complete prescription, even if it calls for but one drug; in fact, the best prescription which can be written will contain but one substance, provided that one meets all the indications of the case.

Usually the prescription is written in the Latin language. The Latin language is preferable for the following reasons: (1) It is established by long custom; (2) it renders it more difficult for the patient to read the prescription; (3) it is the international language of science, and the prescription can be dispensed by a German- or Spanish-speaking apothecary as well as by an English-speaking one. In many

* The metric equivalents given above are those of the United States Pharmacopœia; according to the French Pharmacopœia a teaspoonful equals 5 C.c.

books the statement is made that the Latin language also lessens the liability to mistakes, since every drug has its specific name in Latin. In this country this argument is of small weight, because every substance recognized by the Pharmacopœia has an official English as well as a Latin name, and a prescription written in English, if written entirely in grammatical English, is as correct as one written in Latin; but the ability to use prescription Latin correctly is universally regarded as one of the criteria of an educated physician.

For these reasons, prescriptions are almost universally written in the Latin language, at least so far as the instructions to the apothecary are concerned. The custom has grown up in this country, and I think is a good one, that the directions for the patient which the pharmacist is to copy on the label of the package be written in the English language.

The grammatical construction of a prescription may be most easily explained by the study of an actual example. A prescription if written out in full and translated into the English language would read as follows:

Take
of extract of nux vomica, three grains.
Let pills be made to the number of 12.
Label—One pill three times a day.

It will be noted that the quantity is the object of the verb "take," and, therefore, is in the accusative case. The drugs named are governed by the quantity and are in the possessive case. The word pills is the subject of the imperative make, and, therefore, is in the nominative case. The prescription would be translated into Latin as follows:

Recipe
Extracti Nucis Vomicæ grana tres.
Fiant pilulæ numero duodecimo.
Signa—One pill three times a day.

Rarely, however, in actual practice are prescriptions written in full, and there has arisen gradually a complex system of recognized abbreviations. In abbreviated form this prescription would read:

℞
Ext. Nucis Vom. gr. iii.
Ft. pil. no. xii.
S. One 3 times a day.

As stated in the beginning of this chapter, the best prescription includes but one ingredient if it will meet all the requirements of the case, but frequently it is impossible to accomplish all the desired results with one drug. The following are the reasons or excuses for adding other ingredients to the important one of the prescription:

First—as an adjuvant to assist or strengthen the action of the main drug.

Second—as a corrective to counteract undesirable actions of the main drug; for instance, belladonna is frequently added to cathartic pills to prevent their griping.

Third—to relieve more than one symptom. It is often desirable, even when our treatment is directed to the correction of the underlying cause of the symptoms—that is, to the cure of the disease itself—to make the patient comfortable, by the relief of the troublesome manifestations of the disease; for example, in the treatment of bronchitis, while by administering drugs which by their direct action upon the bronchial mucous membrane we shall eventually relieve the cough, it is sometimes wise to combine with these remedies an agent which will immediately suppress the unpleasant symptom. In the use of this excuse for combining remedies, however, we should be careful not to allow our prescription to degenerate into a mere hodgepodge of symptom-relieving drugs, otherwise they are likely to result in that painful display of therapeutic ignorance known as the "shot-gun prescription."

Fourth—as a vehicle or excipient. Thus certain aromatic substances may be added for their flavoring properties, or water or alcohol to bring the solid drugs into solution, etc. In ordering pills it is generally wiser for the physician not to indicate the excipient for making the pill mass, because the probabilities are that the pharmacist will know better than the doctor which is the best substance to be used for this purpose.

Fifth—occasionally substances are added for the purpose of forming new chemical combinations; for instance, in the old-fashioned embrocation known as lead water and laudanum a chemical reaction takes place with the formation of meconate of lead.

In the writing of a prescription the neophyte will not only render his work of construction much easier, but also be much less liable to error, if he will set for himself a systematic order of procedure and follow it rigidly. The following order of thought is that commonly adopted from long experience.

Let us suppose that a young man suffering with epilepsy has consulted us. Our first thought should be as to the most valuable remedy which we possess for this disease. Without doubt, this is to be found among the bromides, so we choose as our main remedy sodium bromide, and then write it down. The next step is to determine whether there is any other remedy which is useful to assist the action of the bromide, and, after considering the various agents which are employed for this purpose, we decide, perhaps, on antipyrine, which we write down beneath our sodium bromide. We then consider the possibility of undesirable effects from the bromide and remember that they are prone to give rise to an acneiform eruption and that this can be largely prevented by the use of arsenic, so we write below the antipyrine, solution of arsenous acid. It is desirable that the bromides should be given in solution, and as their salty taste is less disagreeable to some when combined with an aromatic, we write down as a last ingredient of our prescription water of peppermint.

Having determined all of the various substances which are to enter into the prescription, the next step is to decide upon the number of doses which are to be ordered for the patient. If our prescription is

written in the English system, the employment of multiples of 12 simplifies the arithmetical calculations, and 24 doses will last a patient about a week, allowing for slight differences between household and apothecaries' measures, so we decide to give a patient 24 doses. The next step is, as our prescription is in the liquid form, to decide the total bulk of each dose. Ordinarily it is desirable to order liquid measures in teaspoonful doses, because this is a measure which is to be had in the humblest cottage. Twenty-four doses of one drachm (teaspoonful) each are equal to 24 drachms, or three ounces; so we direct the apothecary to take enough of the vehicle to make up the three ounces, which translated into Latin reads *Quantum sufficiat ad fluiduncias tres,* which is usually abbreviated, as in the following prescription. At this stage of the proceeding the prescription will read as follows:

℞
Sodii Bromidi.
Antipyrinæ.
Liq. Acid. Arsenosi.
Aq. Menth. Pip. q. s. ad. f℥iii.

It will be noted that up to this point the prescriber has thought nothing of the doses of the drugs employed. This now becomes his task, and each drug is taken up in the order in which it is written on the prescription blank and the quantity to be taken at each dose multiplied by the total number of doses which are in the mixture. Suppose it is decided to administer ten grains of sodium bromide at each dose. The prescriber multiplies, in his head, 10 grains by 24 doses equals 240 grains, or one-half an ounce, which is then put down opposite the sodium bromide.

The dose of antipyrine is ordinarily about five grains; this, multiplied by 24, gives 120 grains, or 2 drachms. This quantity is then set down opposite the antipyrine. The dose of the solution of arsenous acid for this purpose is ordinarily about 2 minims. Twenty-four times 2 equals 48 minims, rather an uncomfortable quantity for the pharmacist to measure, and 2½ minims at a dose is near enough for ordinary purposes and will equal a total of one drachm.

℞

Sodii Bromidi	10 grains by 24 = 240 = half a fluidounce.
Antipyrinæ	5 grains by 24 = 120 = two drachms.
Liq. Acid. Arsenos.	2.5 minims by 24 = 60 = one drachm.

Aq. Menth. Pip. q. s. ad. f℥iii.

These mathematical calculations are of course carried out either in the head or on a separate sheet of paper. If the prescriber adheres to multiples of 12 in his number of doses the computation is sufficiently simple that anyone with ordinary intelligence for figures should be able to carry it out correctly without figuring on paper. The completed prescription as the physician hands it to the patient will be as follows:

MR. JONES.

℞

Sodii Bromid.	℥iv
Antipyrin.	℥ii
Liq. Acid. Arsenos.	f℥i
Aq. Menth. Pip. q. s. ad.	f℥iii

M. S. Teaspoonful 3 times a day in water.—X. Y. Z.

As the language of the prescription is Latin, so must the numerals be in Roman figures. In passing, attention may be called to the fact that in the Latin language the adjective follows the noun. Therefore, in a prescription the numerals always follow the name of the weight or measure, not precede as in English. The Roman numerals have no provision for the writing of fractions, except the fraction ½, which is expressed by s.s., an abbreviation of semissis. Fractions must be written in the Arabic figures, which is perhaps a fortunate circumstance, as it at once calls attention of the compounder to the smallness of the dose.

In writing prescriptions intended for local application we are not so interested in the dose of the drug which shall be represented by a teaspoonful of the mixture as in the percentage concentration, so that our mathematical problem is somewhat different. Suppose, for example, we wish to order half an ounce of a 1 per cent. ointment, the calculation would proceed on the following principle: 1 ounce contains 480 grains, therefore 1 per cent. of 1 ounce would be 4.8 grains, and for ½ ounce it would evidently be ½ of this quantity, or 2.4 grains. For ordinary purposes this degree of exactness is not necessary, and it is the custom to calculate 5 grains to the ounce as a 1 per cent. solution, so that our prescription would be as follows:

℞

Phenolis, gr. ii s.s.
Ung. Aq. Rosæ q. s. ad. ℥s.s.
M. S. Apply locally.

Occasionally we desire to order the strongest possible solution of some drug for external application; for instance, a saturated solution of boric acid is widely used for washing out the nose or eyes. The method of writing such a prescription is as follows:

℞

Acidi Borici q. s. ad. Saturationem.
Aq. Destill. f℥iv.
M. S. For local use.

The directions to the patient, or, as it is technically known, the signature, is a subject deserving of more attention than is usually devoted to it in the study of prescription writing. In the first place, the physician, if he is wise, will not trust to the memory of the patient; that is, he should not depend upon the patient recalling verbal instructions, but should see that definite directions as to how and when

the medicine is to be taken be on the label. Occasionally for certain kinds of local applications, as urethral injections, it is undesirable to have explicit directions on the prescription; in such cases, however, the physician should never have recourse to that reprehensible laches "As directed." This niggardliness of thought has been the cause in the past of the death of more than one patient, and I doubt not has more victims still to come. Not only is the patient liable to forget the directions of the physician unless his memory can be refreshed by the label on the container, but it prevents the druggist from detecting any slip of the pen on the part of the physician which may be a fatal error if allowed to pass. In passing let me urge upon the young physician to always seek the co-operation and interest of the pharmacist, because the druggist is often in a position not only to protect the doctor from the consequences of his mistake, but also to make or mar his reputation in the community. Medicine intended for internal use should without exception contain explicit directions as to the quantity to be taken and the frequency of repetition; if it be a liquid mixture, the dose should be stated in some measure; if it be in the form of pills or powders, the number to be taken at each dose and the intervals at which they are to be repeated should be plainly stated on the label. Prescriptions intended for external administration should plainly say so.

In writing prescriptions in the metric system the details of the calculation are slightly different, but the principle remains the same. For instance, suppose we have a case of intestinal flatulence for which it has been decided to use oil of turpentine. This is best dispensed in the form of an emulsion. An emulsion is a suspension of oil globules in water by means of some viscid substance, ordinarily mucilage of acacia. Following out the line of mental procedure described above, we first put down the ingredients which are to enter into the prescription, which in this case will be oil of turpentine, mucilage of acacia, and water. We have determined that the patient shall take the medicine every three hours and shall have enough to last him a couple of days. This would be somewhere about 10 to 12 doses. In writing metric prescriptions it is necessary to keep the figures always in multiples of ten, otherwise the mental energy required to calculate the dose becomes undesirably complex, so we determine, therefore, to give our patient ten doses to be approximately one teaspoonful each, and for the ease of calculation we shall regard with the European authorities the teaspoonful as equivalent to 5 cubic centimeters; 10 doses of 5 mils each would be 50 mils. It is the custom, and one to be encouraged, in metric prescriptions to have a line on the right-hand side, where the quantities are to be put in, which shall represent the decimal point, just as does the line which is drawn in the accountant's blank book; everything to the left of the line represents grammes, if solids, or cubic centimeters if liquids, everything to the right of the line represents decimal fractions of grammes or cubic centimeters. Moreover, in the metric prescriptions the Arabic figures are preferred to the Roman.

The dose of oil of turpentine is 0.3–0.5 mil. Incidentally the physician who is going to write his prescriptions in the metric system should learn his doses in the metric system. The sight of a young physician learning his doses in the English system and then by complex mathematical processes translating them, for purposes of prescribing, into the metric is a ridiculous monstrosity.

To return to our prescription: we have decided to administer 10 doses, each to contain 0.3 mil of oil of turpentine, or a total of 3 mils. The quantity of acacia required to emulsify the turpentine we leave to the superior technical skill of the pharmacist, simply directing him to take enough. The completed prescription will appear as follows:

℞	Gm.
Ol. Terebinthinæ Rect.	3
Mucilag Acaciæ q. s.	
Aq. q. s. ad	50

M. et ft. emulsionem.
S. Teaspoonful every three hours.

The following are the abbreviations most commonly employed in prescriptions:

ABBREVIATIONS USED FREQUENTLY IN PRESCRIPTIONS.

Abbreviation	Latin	Meaning
Ad	Ad	To; up to
Ad lib.	Ad libitum	At pleasure
Add.	Adde	Add
Aa.	Ana	Of each
Aq.	Aqua	Water
Bull.	Bullians	Boiling
Caps.	Capsula	Capsule
Chart.	Chartula	A paper
Comp.	Compositus	Compound
Cum.	Cum	With
Div.	Divide	Divide
Dispens.	Dispensa	Dispense
Ext.	Extractum	Extract
Ft.	Fiat (fiant)	Let there be made
Fl.	Fluidus	Fluid
Flext.	Fluidextractum	Fluidextract
Gm.	Grammum	Gramme
Gtt.	Gutte	Drops
In.	In	In; into
Inf.	Infusum	Infusion
Liq.	Liquor	Solution
M.	Misce	Mix
Mist	Mistura	Mixture
No.	Numero	Number
	Non repetatur	Not to be repeated
Ov.	Ovum	An egg
Pil.	Pilula	Pills
P.r.n.	Pro re nata	According to circum-
Pulv.	Pulvis	A powder [stances
Q.s.	Quantum sufficiat	Enough
Sat.	Saturatus	Saturated

ABBREVIATIONS—*Continued*

Abbreviation	Latin	Meaning
S. or Sig.	Signa	Label
Sol.	Solutio	Solution
S.s.	Semissis	Half
Sine	Sine	Without
Spir.	Spiritus	Spirit
Stat.	Statim	At once
Tab.	Tabella	Tablet
Tal.	Talis	Such
Tr. or Tinct.	Tinctura	Tincture
Trit.	Tritura	Triturate
T.i.d.	Ter in die	Three times a day
Unc.	Uncia	An inch; ounce
Ung.	Unguentum	Ointment
Vin.	Vinum	Wine
Vit. ov.	Vitellus ovi	Yolk of an egg

Incompatibilities.—The greatest terror of the young prescriber is the thought of incompatibilities; that is, of combining remedies which as a result of some chemical, physical or physiological antagonism shall destroy the efficacy of the prescription. Physiological incompatibilities are rarely complete; in other words, there are almost no drugs which are absolute physiological antagonists; but partial physiological antagonisms are very frequent: sometimes we form them purposely, and the avoidance of them can only be brought about through an exhaustive knowledge of pharmacodynamics.

In pharmaceutical (physical) incompatibility there is no alteration in the chemical composition of the ingredients of the prescription, but some undesirable change in its physical condition. These physical incompatibilities are of two classes—a precipitation through change in the character of the solvent, or liquefaction by the mutual effects of two solids.

When certain solid substances, for instance chloral hydrate and camphor, are rubbed together in a mortar a colorless liquid is produced; that no chemical change has taken place is shown by the fact that when water is added to this mixture the chloral is dissolved and the camphor precipitated. Any two of the following substances when rubbed together are liable to produce a liquid: Antipyrine, camphor, chloral hydrate, ethyl carbamate, menthol, phenol, phenyl salicylate, resorcinol, and thymol. Besides these, acetanilid, acetphenetidin, and salicylic acid are liquefied by chloral hydrate, ethyl carbamate, or phenol.

The most frequent pharmaceutical incompatibilities are, however, those in which some ingredient is thrown out of solution through change in the character of the dissolving medium. Nearly all of the alcoholic preparations of vegetable drugs contain more or less resinous matters, and the addition of water to fluidextracts or tinctures, therefore, usually produces more or less cloudiness. In most instances this is not of great

moment, since although it spoils the elegant appearance of the prescription it generally does not lessen its therapeutic efficacy; but in cases of those drugs whose activity depends chiefly upon some resinous principle, such as benzoin, ergot, guaiac, capsicum, ginger, and the like, the prescriber should always see that the menstruum is strongly alcoholic. Just as water will precipitate a number of substances from their alcoholic solution, so will alcohol precipitate other substances from aqueous solutions. Generally speaking, the inorganic salts are more freely soluble in water than in alcohol, and the addition of the latter to saturated solution of salts is likely to cause precipitation; again, the gums such as acacia are thrown out of solution if alcohol is added in considerable quantities. The "cracking" of emulsions by strong alcohol is due to this precipitation of acacia.

The presence of certain salts increases the solubility of some substances and diminishes that of others; for instance, potassium iodide renders metallic iodine soluble in water, and the volatile oils are separated from their aqueous solution by a number of inorganic salts, notably the bromides and iodides.

It is impossible in a work of this character, as well as useless to attempt, to give a list of all possible chemical incompatibilities. Most of the mistakes of this kind which are made in prescriptions are the result of forgetfulness rather than ignorance. There are a few combinations, however, which are therapeutically so frequently tempting that a list of a few of the more common chemical incompatibilities may not be amiss.

Most of these are in the nature of precipitation of some important ingredient from its solution through the formation of insoluble compounds. Generally speaking, chemical changes do not take place in the absence of water, and pills and powders are much less liable to produce harmful compounds than solutions. There are, however, one or two notable exceptions to this rule. For convenience I have divided the incompatibilities into three groups—those of certain acids, those of certain bases, and a few miscellaneous ones. There are a number of drugs so chemically unstable that they should always be prescribed alone, unless the physician is certain of the compatibility of the combination. These include silver nitrate, the corrosive mercuric chloride, lead subacetate and acetate, the solution of arsenic and mercury iodide, the nitrites, and the solution of hydrogen dioxide.

Acids and Their Salts.—The *mineral acids* are incompatible with salts of the organic acids which they decompose, and with certain drugs containing glucosides, notably digitalis, and, of course, with all the alkalies. The *halogenic acids* and their salts, especially the iodides, are incompatible with oxidizing agents (see below) which liberate their free halogen, and with many alkaloids; a not uncommon and very dangerous combination is that of strychnine with potassium iodide.

Salicylic acid forms precipitates with a number of the salts of iron, notably the ferric chloride, and with the salts of quinine. *Tannic acid*

is chemically incompatible with alkalies, most of the true metals, many glucosidal drugs as digitalis, and the alkaloids; the precipitation of the latter does not take place in highly acid or alcoholic menstrua. It should be remembered that nearly all vegetable tinctures contain at least small amounts of tannin, but enough to react with certain of the more delicate incompatibilities for this agent, especially with the salts of iron; a very common combination of this character is that of tincture of gentian with chloride of iron, which yields an inky black precipitate.

Bases.—The *hydroxides* and the *carbonates* are incompatible with acids and acid preparations (the following contain considerable amounts of acid, enough to react with the carbonates: fluidextracts of ergot, nux vomica, and sanguinaria, syrups of orange, ipecac, squill, and the hypophosphites, solution and tincture of iron chloride, Basham's mixture and the solution of hydrogen dioxide), with practically all of the salts of the alkaloids, which are precipitated in their insoluble basic form, with the salts of lime, magnesium, and lithium and of the heavy metals, with tannic acid, and with chloral hydrate.

The *alkaloids* are precipitated from their aqueous solution by tannic acid, iodine and the iodides (some of them also by the bromides), and corrosive sublimate. Strychnine is an especially easily precipitated alkaloid, being thrown out not only by the iodides, but also by the bromides and the chlorides. *Antipyrine* is chemically an alkaloid and is precipitated by the same reagents; it is further incompatible with the ferric chloride and with the nitrites. The latter combination is deserving of special note, because one is frequently tempted in febrile conditions to combine antipyrine with the sweet spirits of nitre, which yields a greenish isonitroso-antipyrine.

The soluble *ferric salts* have a wide range of incompatibilities, and the inexperienced had probably better avoid attempts at combinations. The more important of their incompatibilities are with the alkalies, with tannin—and therefore nearly all vegetable fluidextracts and tinctures—with the alkalies, with substances belonging to phenylic series (including phenol, salicylic acid, benzoic acid, cresol, etc.), with which it produces color reactions and sometimes precipitations, and with many of the volatile oils.

Miscellaneous.—*Chloral hydrate* and *chloralformamid* are decomposed by alkalies, liberating chloroform. Concentrated alcohol will also form with chloral hydrate a substance commonly known as chloral alcoholate. The *oxidizing agents* (which include potassium permanganate, potassium chlorate, hydrogen dioxide, nitric acid and the nitrates, and a number of unofficial substances as the various peroxides and perborates) form with reducing agents (which include the salts of the halogenic acids, and all organic substances) in the dry state explosive compounds, the most familiar examples of which are gunpowder and nitroglycerin, the former being the result of combining potassium nitrate with charcoal, and the latter nitric acid with glycerin. Gen-

erally speaking, in fairly dilute solutions there is little danger from these mixtures. The oxidizing agents also, as already noted, liberate the free halogens from solutions of the bromides, iodides, and chlorides.

MODE OF ACTION OF DRUGS.

Drugs may affect a function not only directly, but also by causing alterations in some other organ of the body which lead to modifications in the function of the first organ. For example, digitalis, in certain conditions, by stimulating the heart, thereby improving the circulation in the kidney, may lead to a larger secretion of urine; or, again, by violent purgation we may diminish the amount of liquids in the body and thus lessen the flow of urine. Drugs influencing functions in this manner are said to possess an *indirect action.*

For a drug to exercise a direct action upon any organ it is necessary that it come in immediate contact with that organ. In the case of the greater number of organs of the body, drugs can be brought in contact with them only through the blood stream, so that, while in a sense all physiological effects are local actions, there is a justification for the old terms of *local* and *general* or systemic action. By the former is meant the effects produced by drugs at the point of the body with which they first come in contact, generally in comparatively concentrated solution; the systemic effects are those changes which are produced in distant organs to which the drug is carried by the blood stream.

It is evident that for a drug to exercise a general action it must enter the circulation, and the process by which the drug enters the blood stream is spoken of as *absorption.* The system tends to free itself from all foreign or unnatural chemicals, and hence drugs which have once been introduced into the system after exercising their influence are more or less rapidly thrown out; this process is known as *elimination.* During their sojourn in the system they may or may not undergo alteration in their chemical structure. (For consideration of channels of absorption see Modes of Administration, page 24.)

The channels of elimination may be any or all of the secretory organs of the body. The most important are the kidneys, but the glands in the alimentary tract are important excretory organs for a number of poisons, while the glands in the mucous membrane of the lung may excrete certain volatile drugs, so that they appear in the exhalations.

Under the term drugs must be included not only those substances which directly influence the bodily functions—that is, which possess physiological action—but also any material substance which is used for the treatment of disease. In some instances the beneficial action of the drug is purely mechanical; thus, bismuth subcarbonate, which is non-absorbable and has almost no direct action upon the intestinal tract, is valuable in certain conditions of inflammation of the alimen-

tary canal, because, being a heavy insoluble powder, it clings to the mucous membrane and mechanically protects it against irritating substances.

Other agents act by some relatively simple chemical or physicochemical process not directly affecting the functions of the body, but correcting rather the results of disordered function: for instance, the alkaline carbonates are used to neutralize excessive acidity in the stomach; certain substances which have the power of dissolving animal tissue are used as caustic agents—that is, to destroy undesirable growths.

A third group of remedial agents which do not affect directly bodily functions includes those substances which are used for the purpose of destroying living causes of disease. This would include such groups of drugs as the disinfectants, substances which are used to destroy bacteria; or the anthelmintics, drugs which are used to get rid of intestinal parasites.

HOW DRUGS PRODUCE PHYSIOLOGICAL EFFECTS.

But of all the agents which are used for the relief of disease the most important, and the most interesting, are those whose value depends upon their power to produce alterations in the functions of various organs by a process which we may speak of as a physiological action, as opposed to chemical or mechanical effects of the type just described. The way in which these drugs produce alterations in function has been the subject of much speculation and research, but, while the observed facts render highly probable certain theories concerning the mode of action of these agents, we can hardly pretend to have definite knowledge on this subject. A mistake which has been made in discussing this subject is to approach it with the idea that all of these agents act in the same manner. Such is certainly not the case. We distinguish at present at least three methods in which drugs affect various functions of the body, and it is not improbable that there are others.

A number of crystallizable salts when introduced into the body, altering the molecular concentration of the bodily fluids, by the laws of osmosis change either the direction or rapidity of the flow of the liquid constituents of the body, thereby leading to various departures from normal function. This constitutes what is generally known as salt action, which is considered in more detail on page 21.

A second group seems to act largely by virtue of local irritation. For instance, many agents which, when applied in concentrated form to mucous membranes, produce acute inflammatory conditions when introduced into the blood stream in smaller quantities excite certain organs, especially glandular structures, to abnormal activity. It is noteworthy, however, that most of these drugs if used too freely become so irritant as to destroy vitality of protoplasm and thus lessen, and often permanently impair, functional capacity.

Other drugs seem to unite chemically with some portion of the cell protoplasm, forming compounds which respond to physiological stimuli differently from those of the normal cell. These unions vary in the degree of their stability; generally speaking, they are very loose compounds, so that it is possible to readily separate, for instance, the alkaloids from the tissues of the body. In some cases, however, the union seems to be so firm that it cannot be broken up without destruction of the drug molecule.

There are some substances which are capable of uniting with nearly any of the tissues of the body. These substances, which are generally spoken of as protoplasmic poisons, exercise a wide range of influence. The majority of chemical agents, however, which are used in practical therapeutics show a marked predilection for one or another type of protoplasm; thus, one drug affects especially nerve-centers and another muscle-fiber, and so on. This tendency to choose one group of tissue is known as the "selective action."

The present concept of the mode of action of drugs is that it is essentially of chemical nature; that the drug combines with some portion of the cell contents, thereby modifying the chemical processes within the cell which are at the basis of its vital activity. The cell is not to be conceived of as a homogeneous mass of protoplasm, but may be more aptly compared to a complex emulsion containing probably several chemically distinct bodies. Our knowledge of cellular physiology is too imperfect to allow us to formulate any very lucid hypothesis of the manner in which drugs modify cell functions. It is noteworthy, however, that drugs can produce only three effects upon cell function—increase, diminution, or destruction. A pleasing speculation of the mode of action of drugs has been suggested by Curci in connection with the aliphatic narcotics. His conception is that each of the ganglionic cells of the brain consists of a number of particles of organic matter, from a reaction between which arises the nerve current; the effects of the narcotic are not due to its action on these particles but, by being dissolved in what we may speak of as the interstitial fluid, it interposes a resistance to the passage of nerve currents between vital particles of the cell. A crude simile may be found in the case of the cell of the electric battery; if we interpose between the metal plates a non-conducting fluid we destroy, or at least greatly weaken, the amount of the current which that cell gives off.

There is nothing known concerning the action of drugs which forbids the extension of a somewhat similar theory to other portions of the body. The exaltation of function in any nerve-cell can be conceived of as due to a better communication between the essential molecules of cell activity, and the same sort of reasoning may be applied to muscle- or gland-cell.

While the hypothesis suggested above is hardly more than speculation, there is strong evidence that at least in many instances the alterations in function produced by chemical agents are consequent upon

a union between those agents and some portion of the cell contents. If this union be of a permanent nature it must evidently produce permanent changes in the activity of the cell, but since in the great majority of instances drug effects are but temporary and the agents which cause them are after a few hours thrust out of the system it is evident that the combination must be a comparatively loose one, and that the drug will begin to separate from the cell protoplasm the moment the fluid which bathes the tissues is entirely free of the poison. An analogous condition is the freedom with which hæmoglobin takes up or gives off oxygen according to the condition of the surrounding medium.

If the theory that many drugs produce their effects by forming chemical union with the protoplasm be correct, then we should find that substances of similar chemical composition exercise similar effects upon the body. Such, indeed, is the fact, and, while there are many apparent exceptions to this law which are inexplicable with our present knowledge, so many facts which a few years ago seemed incomprehensible have been shown to support rather than contradict the close relation between chemical structure and physiological action that it is probable that as our knowledge of physiological and pharmacological chemistry increases so will the number of these apparent exceptions disappear. Another interesting confirmation of the theory of the chemical action of drugs is found in the fact that the same kind of tissues in various portions of the body are usually acted upon in the same manner. For instance, pilocarpine slows the pulse, increases the secretion of sweat, and causes contraction of the pupil, actions which at first glance would seem in no way related to each other; but all of these effects are brought about through the action of the drug on the peripheral endings of a certain type of nerves, all of these structures being supplied with the same sort of nerves.

Drugs may either increase or lower functional activity; the terms stimulation and depression are generally applied to these two changes respectively. The word stimulation, however, is used to convey two entirely different concepts. If an electrical current is applied to a nerve in order to make the muscle contract, physiologists commonly speak of "stimulating the nerve," although the term irritation would be more accurate; in a similar way certain chemical agents, that is drugs, may excite an organ to functional activity by a species of chemical irritation. On the other hand, there are a number of drugs which exalt the functional capacity without necessarily calling forth an outburst of functional activity; for instance, strychnine stimulates the spinal cord in the sense that it heightens the responsiveness of the reflex centers, but the evidence of this increased functional activity is manifest only when these centers are excited by some external agent. It is necessary to distinguish carefully between these two kinds of stimulation, for it is evident that the first kind, the excitation to kinetic action, necessarily leads to an output of energy and tends towards the

production of exhaustion, while in the second type of stimulation there is not necessarily any increase of function, but only the capability for better function if circumstances demand it.

It is similarly necessary to distinguish carefully between depression, suppression, and exhaustion. The evidences of normal or even exaggerated function may be entirely suppressed by a drug which exercises no action whatsoever upon the organ in question; for instance, curare, through its paralytic action on the peripheral motor nerves, suppresses the convulsions which are ordinarily caused by strychnine, but it does not depress the spinal centers. The differentiation between depression and exhaustion is of great moment from a clinical standpoint, because the method of restoring function to a depressed organ is absolutely different from that which would be appropriate for an exhausted organ.

Stimulation and depression in the pharmacological sense are directly antagonistic effects, and we find those drugs which are depressant tend to counteract the influence of those which are stimulant, and *vice versa*. This antagonism is not always, however, absolute, for in the end the depressant will nearly always overcome the stimulant. If the dose of the depressant be small, function may be restored to the organ by means of a stimulating remedy, but if the dose be too large the stimulant is not able to overcome the depression; on the other hand, no matter what the degree of stimulation, we may lower function by the use of depressants. It is possible that the failure of stimulants to overcome the effects of large quantities of a depressant is due to the fact that almost universally those remedies which in appropriate dose increase function in toxic quantities diminish it. Drugs whose actions are in the same direction—two stimulants or two depressants—are called synergists; those of opposite directions, as a stimulant and depressant, are called antagonists.

THEORY OF IONIC ACTION.

Drugs may be divided into those of organic and inorganic origins, and these terms frequently occur in medical literature. This division is unsatisfactory to the pharmacologist; thus the chemist would class potassium oxalate or amyl nitrite as organic compounds, but pharmacologically they are more nearly related to drugs of mineral origin. A much more useful division from the medical standpoint is into electrolytes and non-electrolytes. These differ essentially in that the former under certain conditions may be split up into their constituent parts, or ions as they are called, whereas the latter cannot be further subdivided without destroying their identity.

When an electrolyte, for instance sodium chloride, is dissolved in water, it exists in the solution not merely in the form of the salt, but also as its constituent ions or electrons, in this instance sodium (kation) and chlorine (anion). This separation, which is called dissociation or

ionization, is to be sharply differentiated from chemical decomposition: no evidence of free chlorine or free sodium can be detected chemically in a solution of sodium chloride. The proof that such dissociation takes place is found in the changes of the physical properties of the solution of the salts. The addition of a salt to water lowers its freezing point, and the amount of lowering is proportionate to the number of molecules which are dissolved in the water. Now it has been found that the lowering produced by dissolving weighed quantities of certain salts is much greater than should be expected from the number of molecules in the original salt. In other words, more molecules have been dissolved than were placed in the water. In the same way we find that there is an excessive increase in the electric conductivity of the fluid and in the boiling point. A plausible explanation of these facts would be that when sodium chloride dissolves, the two elements dissociate and exist in the water not as one large molecule, but in the form of two molecules.

As the solution of a salt is evaporated the dissociated ions unite again to form the salt. This takes place, probably not all at once, but gradually, because it has been found that the more concentrated the solution the less the proportion of ionization.

In the same way that the process of ionization is not to be confounded with chemical decomposition, so must the ion be kept distinct from the chemical element. In the instance quoted—that of sodium chloride—the ions correspond to elements, but in other instances they may contain several elements. For example, sodium bicarbonate dissociates in the following manner: $NaHCO_3 = Na + H + CO_3$, or ammonium sulphate dissolves as follows: $(NH_4)_2SO_4 = 2NH_4 + SO_4$.

The effects of many drugs depend upon their dissociation. For instance, hydroxyl is destructive to animal tissues, and we find that all the inorganic compounds containing this group, as NaOH, KOH, and NH_4OH, show a caustic effect. On the other hand, when this radical is combined in an organic molecule in such a way that it does not ionize, as for instance in alcohol (C_2H_5OH), the caustic power is no longer manifest. Again, the salts of cyanogen, as potassium cyanide, are deadly poisons, but potassium ferrocyanide ($K_2Fe(CN)_6$) is harmless, because when it dissociates the cyanogen ion is not liberated, but the breaking up is in the following manner: $K_2Fe(CN)_6 = 2K + Fe(CN)_6$.

The physiological effect of an electrolyte will be the sum of the actions of all its constituent ions; for instance, ammonium bromide has certain physiological properties in common with potassium bromide, on the one hand, and certain relations to ammonium iodide on the other, but differs from each. Generally, however, one ion is so much more powerful that it entirely dominates the action of the compound. Thus in strychnine sulphate the sulphuric ion is so much feebler than the strychnine ion that the action of this salt cannot be distinguished from any other salt of strychnine. It may be the kation,

as in the instance just quoted, or it may be the anion, as in the case of potassium cyanide, which is the predominating.

Besides their ionic effects, however, crystallizable substances exert what is known as a "salt action." This latter effect depends upon the law of osmosis. When distilled water is separated from a solution containing a crystalloid, as an inorganic salt, by a semi-permeable membrane, there result two currents: the water on one hand passing through the animal membrane into the saline solution, and the salt on the other hand passing out of its concentrated solution into the water. This process continues until the solutions on the two sides of the membrane have the same concentration; that is, until they are isotonic. In the same way, if two solutions of the same salt in unequal concentrations are separated by a semi-permeable membrane, the water from the more dilute solution will pass into the more concentrated one,

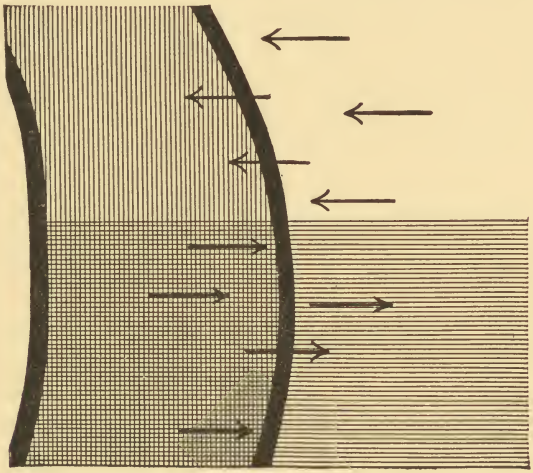


FIG. 1.—Diagram to illustrate salt action: When the molecular concentration of the salts in the blood-vessels becomes greater than that of the surrounding tissues, there is a passage of salts out of the vessels and water into the vessels until the concentrations on the two sides of the vessel walls become the same.

and the salt from the latter will pass through the membrane into the more dilute solution until the two become equal in density. When a concentrated solution of any crystalloid is introduced into a body cavity, as the intestines, in large enough amounts, this process takes place, and there is a determination of water from the bodily tissues into the intestines, and a passing out of the salt from the intestines into the surrounding tissues, until the intestinal contents become nearly isotonic with the body fluids. In the same way, when the concentrated salt enters the blood-vessel there will be a determination of fluid from the surrounding tissues into the vessel until the blood stream again becomes isotonic.

It must be remembered that not only salts, in the chemical sense of

the word, influence osmosis, but any crystalloid, as sugar or urea, has the same effect, and that, therefore, many substances which are not salts, properly speaking, still exercise a salt action.

If the drug contains an ion which is very potent, the salt action will be insignificant, because we are unable to introduce a large enough dose of the salt to influence the osmotic equilibrium of the blood without killing the patient by the effect of the toxic ion.

CIRCUMSTANCES MODIFYING THE ACTION OF DRUGS.

The degree of effect produced by any chemical agent on the system will manifestly depend, first, upon the relative susceptibility of the organ upon which it acts at the time of its exhibition, and, secondly, on the relative quantity which comes in contact with the organ. The amount which reaches the organ depends primarily on the amount administered—that is, the dose—but secondarily on a number of other conditions.

It should be emphasized that it is impossible to set down any absolute dose for any drug; the quantity given must be varied with each individual patient. When giving drugs which have a definite physiological action, especially when using them in immediately serious conditions, the physician should be limited in the amount he gives only by the effects produced. As a recent writer put it, "the dose of a drug is enough." It is necessary, however, for the beginner to learn for each drug the quantities which shall represent the amount or dose to be used in ordinary conditions. The most important circumstances which modify these doses are as follows:

Age.—Generally speaking, persons in the prime of life can stand larger quantities of drugs in proportion to their weight than those at either extreme. The most important modification, however, of the dose necessitated by the age of the patient is as regards children. Speaking in a broad way, for the majority of drugs the dose for a child is proportionate to the bodily weight. The various rules, such as those of Young and of Cowling, which are employed to calculate the dose for children are simply methods of estimating the weight of the average child at a given age. For instance, Cowling's rule, which is the more accurate as well as the simpler of the two, is that the dose for a child is that fraction of the adult dose which is obtained by taking the age of the child at the next birthday and dividing by 24—for instance, a child of seven years old would take 8/24 or ⅓ of an adult dose; this simply means that the child of seven weighs, on an average, one-third the average adult, or about 50 pounds. While these rules for estimating the dose of children are sometimes serviceable, the author is convinced that it is much more accurate, and not much more troublesome, to determine the actual weight of the child. As a well-known pediatrist recently remarked, we are much kinder to laboratory animals in regard to the question of dose than we are to children. In calculating the dose for a child based upon its weight

we consider the weight of the adult as 150 pounds and give a child such a fraction of the adult dose as its weight is of 150 pounds. Thus, a child of 75 pounds would take half of the adult dose, or a child of 50 pounds one-third of the adult dose.

There are some notable departures from the weight rule in calculating the dose for children. The central nervous system of the child, and especially of the young infant, is hyper-sensitive to the action of drugs, and thus substances which act upon the central nervous system must be given in much smaller quantities than would be determined by the weight rule. Especially does this apply to morphine and its congeners. On the other hand, those drugs which act upon the alimentary tract can be given in proportionately much larger dose for children than adults.

Weight.—For adults the dose must often be modified according to the size of the patient; it is an absurdity to give the same dose to a delicate woman of ninety pounds as to an athletic giant of three hundred pounds simply because they have both reached maturity. In regulating the dose according to the weight of the patient, however, it must be remembered that adipose tissue contains a small proportion of blood; corpulent persons, therefore, will take smaller quantities in proportion to their weight than the lean.

Constitution.—A number of factors which more or less modify the personal responsiveness toward drugs may be grouped together under this general term. Persons born and bred in comparative luxury are generally more susceptible to the action of drugs than those whose station in life has exposed their constitutions to the hardening influences of the daily struggle for existence.

Under this head may also be included that peculiar factor of which we understand absolutely nothing, but which we call idiosyncrasy. There are certain individuals who for some entirely unknown reason show an extraordinary susceptibility to the actions of certain drugs. Generally it will be found that these patients are susceptible, not to what we may speak of as the therapeutic action of the drug, but to the toxic effect; thus I have seen less than a drachm of compound tincture of cinchona cause a dermatitis. These peculiar susceptibilities are impossible to foresee. It is well for the physician, therefore, to listen to the statements of the patients concerning these peculiarities, for while at times the statements, especially of neurotic individuals, of their peculiar susceptibility to certain drugs are not in accordance with the facts, the physician who disregards these statements completely may at some time work irreparable damage with the incautious use of remedies.

Disease.—Of all the influences which modify the effects of drugs, the most important is the existence of disease. Not only do the effects of drugs in conditions of disturbed functions differ quantitatively, but also qualitatively. Thus antipyrine has in the healthy individual no effect on the temperature of the body, but in febrile states may lower

the temperature so suddenly and so greatly as to induce collapse; again, it is well recognized that the influence upon the heart of such drugs as digitalis is much less when the body temperature is high than in normal persons. Disease may either increase or diminish the susceptibility of various organs to the influence of drugs. In the first place, where there is acute inflammation of any organ it is usually more susceptible, especially to the effects of stimulating remedies; thus in cases of acute nephritis such a drug as turpentine, which ordinarily simply stimulates the kidneys to greater activity, may prove so irritant as to lead to a diminution instead of an increase of function. On the other hand, in passive congestions, which are sometimes spoken of as chronic inflammations, frequently there is a reduction in the susceptibility to the chemical influence.

In a number of diseases, especially those of bacterial origin, the symptoms are caused by the effects of certain poisons produced within the system. The mode of action of these toxins of disease seems to be precisely analogous to that of our ordinary remedial agents, and just as a depressant drug may antagonize a stimulant remedy or synergize a depressant one, so may these toxins act either with or against the remedy. For instance, the vasomotor center depressed by the toxin of pneumonia requires much larger doses of stimulants to excite it to normal activity than would the normal vasomotor center to be excited to excessive function.

Under this general head may also be included the effects of drug habits upon the susceptibility of the patient. Speaking generally, persons who have been accustomed to the use of large quantities of either alcohol or opium are more resistant to the effects of nearly all drugs, but especially to those which act upon the central nervous system.

Mode of Administration.—It is evident that, other things being equal, the larger the amount of drug which is in the blood stream at any given moment, the greater will be the degree of its action, but the quantity present in the bodily fluids at any given time will depend not merely on the size of the dose exhibited, but also on the ratio between rapidity of absorption and the rapidity of elimination. Since remedial agents are absorbed more rapidly through some channels than through others, the degree of effect will manifestly vary according to the way the drug is given.

There are seven channels through which drugs are introduced into the blood stream. These are: injection into a vein; injection into muscular tissue; injection into the subcutaneous cellular tissue; administration by the mouth; introduction into the rectum; application to the skin, and by inhalation.

Under ordinary circumstances the administration by the mouth is always given the preference for the following reasons: In the first place, it is by far the simplest method; secondly, the drug is exposed to the solvent action of a variety of fluids, such as the dilute acid of

the stomach, the dilute alkali, and the fat of the intestines; and, finally, absorption is generally fairly rapid and complete.

When a very quick action is desired the drug should be administered either hypodermically or intra-muscularly; absorption from the muscular tissue seems to be decidedly more rapid than from the cellular tissue. For hypodermic injection the drug must be in complete solution in an aqueous menstruum, must be perfectly sterile, and not too highly irritant, otherwise the injection is likely to give rise to troublesome abscesses. There are, however, a few insoluble substances which are sometimes injected hypodermically.

When a substance is thrown directly into a vein its action is almost instantaneous, for it will reach the most distant portions of the body within a period of thirty seconds. Because of the troublesomeness of the method and the seriousness of the results of any lapse of technique, this method of administration is but rarely employed.

The rectum was not intended by Nature as an absorbing surface, and the entrance into the system through this channel is both slow and uncertain. It was at one time believed that drugs administered by the rectum exercised a disproportionate influence upon the pelvic structures, but a moment's consideration will show that this is physiologically impossible, since for a drug to reach the bladder, for example, after rectal administration, it is necessary for it to be carried through the venous circulation up to the heart and from the heart out through the arteries to the bladder. Rectal administration is, however, sometimes valuable in cases where the patient is unable to swallow or in cases of vomiting where the drug is immediately expelled after swallowing. For rectal administration drugs may be given as an injection dissolved in water, or in the form of a suppository.

The so-called endermic method—that is, the introduction of drugs through the skin—is applicable, first, to volatile substances, and, secondly, to those which are soluble in both fat and water. The rate of absorption, however, is extremely variable and the method is of little service except with a few remedies which are prone to disturb the stomach.

For a drug to be absorbed through the mucous membrane of the lungs it must be, first, volatile at the body temperature, and, secondly, not too highly irritant to be respirable. The most familiar examples of pulmonary absorption are in the case of surgical anæsthetics. Absorption through the lungs is extremely rapid because of the delicacy of the mucous membrane and the richness of the vascular supply.

CHAPTER II.

DRUGS USED TO AFFECT SECRETION.

DIURETICS.

The quantity of urine secreted by the kidney depends upon the functional state of the kidney epithelium and upon the amount of blood passing through the renal artery. The quantity of blood which flows to the kidney will evidently be influenced (1) by the total quantity of blood in the body, (2) by the velocity of the blood current, and (3) by the relative size of the renal artery and the general arterial system. It is evident, therefore, that the mere elevation of the blood-pressure *per se* will not increase the flow of urine—except where there is an obstruction within the kidney to the circulation, as in the case of interstitial nephritis—because if all the blood-vessels of the body contract simultaneously, while the blood-pressure is raised, the amount of blood which is pumped by the heart in a given period of time—that is, the velocity of the blood stream—will be diminished, and if the constriction of the renal vessels is equivalent in degree to that of the other vascular areas, the amount of blood which passes through the kidney will actually be diminished because of the slowing of the blood stream. On the other hand, if the arteries in the great vascular areas contract and that of the kidney dilates, or remains at its normal size, it is evident that the blood will be squeezed out of the rest of the body into the kidney, so that this organ will receive an abnormally large amount of blood, and the quantity of urine will therefore be increased.

The fact that the general vasomotor constriction diminishes the flow of urine is seen in the action of such substances as ergot, in some cases of polyuria, and also in the frequent failure of diuretics of the digitalis group to increase the urine unless combined with a vascular dilator, as sodium nitrite.

In accordance with the above, we may divide the diuretics into three groups: (1) those which by virtue of a salt action increase the volume of the blood, the saline diuretics; (2) those which directly stimulate the secretory epithelium, the stimulant diuretics, and (3) those which increase the blood-pressure. The latter group will be considered under the cardiac stimulants. It includes digitalis, strophanthus, squill, and apocynum.*

Diuretics are used for the following purposes:

(1) *To maintain the action of the kidneys.*—It is hardly necessary here to discuss the necessity of excretion to the system. In various kidney diseases this indication is very urgent; but, as the lessened excretion too often depends upon a profound organic altera-

* Most of these drugs are also more or less stimulating to the kidney epithelium.

tion of the renal secreting structure, it is evident that very frequently diuretics must fail when most needed. Moreover, it must be remembered that an unhealthy kidney is abnormally sensitive, and what in a healthy organ may act as a stimulant, in nephritis may become irritant and diminish instead of increase excretion. When lessened urinary excretion is purely functional in its origin, diuretics are most serviceable. In fevers especially is it necessary to maintain the action of the kidneys; for this reason water should always be freely given during fever.

(2) *To evacuate fluid.*—In using diuretics for the purpose of getting rid of dropsical effusions a sharp distinction must be made between those cases of œdema which depend chiefly upon failure of the kidney and those cases in which this organ is perfectly healthy. In renal dropsy only the milder diuretics should be employed, on account of the danger of increasing the inflammation of the kidney. On the other hand, in dropsies of cardiac origin in which the kidney is not affected at all larger quantities of the fluid can be eliminated from the system with less exhaustion through the kidney than through any other channel.

(4) *To eliminate poisons from the blood.*—The diuretics are useful to aid in the elimination of endogenous poisons, such as those of gout and kindred disorders, as well as poisons entering the system from without, as alcohol and lead. The belief which is widespread among clinicians that the toxins of bacterial diseases can be eliminated through the kidneys has not received any firm scientific substantiation. It is probable that the benefit which results in these cases from the free use of water is due to the dilution of the poison and to the neutralizing of the irritant effects upon the kidneys which would tend to prevent the excretion of toxic metabolites rather than to any increase in the excretion of bacterial toxin.

Certain substances are used for their local action upon the mucous membrane of the urinary tract rather than for any effect in increasing the quantity of urine. In the narrow sense of the word these substances cannot be called diuretic, but as many of them possess more or less diuretic power, and because of the fact that they are so frequently used in conjunction with the diuretics proper, it is more convenient to consider them under this head.

EFFECTS OF WATER.

By increasing the volume of blood the ingestion of large amounts of water tends to augment all the secretions, but especially those of the kidney. Whether the water shall affect the volume of the urine or of the sweat depends upon several circumstances, especially upon the temperature of the patient's surroundings.

A matter of great importance in this connection is the effect of the ingestion of water upon the elimination of the solid constituents

through the urine. Although some of the older investigators failed to obtain any increase in the total amount of nitrogenous material eliminated through the use of water, the preponderance of testimony is so strong that it must be considered as proven that, in ordinary conditions, not only the total bulk of urine but also the quantity of solid matter is increased by the administration of water. Whether this increase of urinary solids betokens a more active metabolism, or whether it merely indicates a washing out of already formed waste products, cannot be so definitely answered. Many authorities maintain that the increase in solids is simply the result of flushing the system, and that, if the administration of water is continued, the primary augmentation of solid matter gives way to a marked decrease in the urinary nitrogen after the accumulated products of metabolism have been flushed out. On the other hand, the experiments of Landauer, and of Edsall, and others, indicate strongly that, while the solid matter eliminated is largely stored-up waste products, there is also a distinct, if slight, increase in the destruction of proteid tissues.

Water may be used as a diuretic in all of those conditions in which this group of remedies is indicated save in the treatment of dropsy. It would seem unnecessary to point out the irrationality of the hypodermic injections of physiological salt solution in circulatory failure combined with œdema were it not for the fact that it is still sometimes done.

For medicinal purposes, water may be introduced into the system through one of three channels: the alimentary tract, subcutaneous tissue, or intravenous injection. In cases where rapidity of action is not essential and the stomach not rebellious, for obvious reasons it is generally preferable to have the patient drink large quantities of fluid. Where rapid absorption is desirable we may have recourse to either the hypodermic or intravenous injection of physiological salt solution. For this purpose one may use a 0.9 per cent. solution of sodium chloride, although many prefer the more complex Ringer's fluid which contains also the potassium and calcium ions in approximately physiological proportions. These injections may most easily be given with some type of fountain syringe and the temperature should be slightly above that of the body. The strictest asepsis should of course be observed throughout the whole procedure. In cases in which it is desirable to maintain a continuous supply of water over long periods of time without using the stomach, as, for instance, after abdominal operations, recourse may be had to the proctoclysis as suggested by Dr. Murphy. In this method physiological salt solution is introduced from a fountain syringe into the rectum at the rate of about one drop per second. Large quantities of fluid can be administered to the patient in this manner with an extraordinarily small amount of discomfort.

In circulatory failure due to hemorrhage or surgical shock the intravenous injection of physiological salt solution is of great service to maintain the heart's action through the influence of vascular resistance. As a circulatory stimulant, however, in cases of essential heart-failure

or in the presence of cardiac depressant poisons, the value of the treatment is far less certain. Water has also been highly recommended as the means of aiding the elimination of many poisons, especially of bacterial toxins. The evidence, however, that the excretion of these substances through the kidney may be increased is very unsatisfactory, to say the least.

SALINE DIURETICS.

If a concentrated solution of a non-toxic crystalloid enters the blood stream, it will attract water from the rest of the body in order to maintain the proper concentration of the blood, and hence increase the volume of fluid in the blood-vessels. On the other hand, if a large amount of either an isotonic or a hypotonic solution is injected into the blood, it will retain a large amount of the water in which it is dissolved, so that again the volume of the blood will be increased, and hence the injection of either concentrated or dilute saline solutions into the blood stream provokes diuresis. The saline diuresis, however, is not a purely passive one for it has been shown that there is an increased consumption of oxygen by the kidneys which infers a greater activity of the renal secreting structures.

It is evident that if the salt is one which is readily diffusible, however, there will be a large escape of salt from the vessel, so that the amount of fluid attracted into the vessel will be comparatively small, and for this reason readily diffusible salts are less powerful diuretics. On the other hand, a salt of too low a diffusibility will not be absorbed through the intestinal mucous membrane, and, remaining in the bowel, act as a cathartic and not as a diuretic. According to the ideas of Pauli, the rapidity with which the inorganic salts pass through living animal membranes is in inverse proportion to their activities as precipitants of protein matters.

While the diffusibility of the official salts is generally determined by the acid radicle, the base with which they are combined is not altogether a negligible factor. Thus, the salts of sodium are rapidly diffusible, so that they are of less value either as cathartics or diuretics, although by combining sodium with some sparingly diffusible acid, as sulphuric acid, one may form even cathartic salts. Magnesium salts are all very poorly absorbable and, therefore, act, when taken by the mouth, as cathartics. Midway between these two extremes stand the salts of ammonium, potassium, and lithium, and it is chiefly with one of these three bases that we would look for the important diuretic salts. Pauli gives the order of diffusibility of the common bases as follows: potassium, ammonium, magnesium. Of the acid ions: iodide, chloride, acetate, tartrate, citrate, and sulphate.

From a practical standpoint, salts useful as diuretics are:

1. All the non-toxic salts of potassium and of lithium.
2. Ammonium acetate.
3. Sodium citrate and possibly the acetate.

POTASSIUM.

With many of the official combinations of potassium with inorganic acids the activity of the combination depends chiefly upon the acid ion. The salts which are considered in its place are those which owe their therapeutic utility either to the potassium ion or to a salt action.

Materia Medica.—*Potassium carbonate,* the potash of commerce, is obtained from wood ashes and other sources. The crude carbonate occurs in the form of huge stony masses, but when purified so as to conform to the U. S. Pharmacopœia it is a white granular powder, very deliquescent, without odor and with a simply alkaline taste. It is soluble in less than its own weight of water, but insoluble in alcohol. It is too irritant for general use as an internal remedy.

Potassium bicarbonate, which because less irritant is much to be preferred therapeutically to the carbonate, is in the form of transparent colorless crystals, not deliquescent, slightly alkaline in reaction, soluble in about 3 parts of water, almost insoluble in alcohol.

Potassium hydroxide is usually found in the form of white or nearly white semi-translucent pencils, very freely soluble in water and in alcohol. It is an active caustic. It is rarely used internally, and then only in the form of the solution.

Potassium citrate is found either in crystalline form or as a white granular powder. It is deliquescent in air, freely soluble in water, sparingly so in alcohol. Its aqueous solution reddens litmus paper, but does not affect phenolphthalein. It is the least offensive to the palate of all the potassium salts except the tartrates.

Potassium acetate, which occurs either in crystalline masses or as a white powder, is extremely deliquescent and soluble in less than half its weight of water, also freely soluble in alcohol. Its solution reacts alkaline to litmus, but does not affect phenolphthalein.

Potassium bitartrate, or cream of tartar, differs from the other official salts of potassium in that it is practically insoluble in water, requiring 200 times its weight of water (77° F.) to dissolve it. It is acid in reaction, and has a pleasant acidulous taste. On account of the relatively large proportion of tartaric acid present it is an active hydragogue cathartic. (See p. 270.)

Official Preparations.—The following are the official preparations whose activity depends chiefly on the potassium ion:

Potassii Acetas	15 to 30 grains (1–2 Gm.).
Potassii Bicarbonas	15 to 30 grains (1–2 Gm.).
Potassii Bitartras [Cream of Tartar]	15 to 45 grains (1–3 Gm.).
Potassii Carbonas	5 to 10 grains (0.3–0.6 Gm.).
Potassii Citras	15 to 30 grains (1–2 Gm.).
Potassii Citras Effervescens (20 per cent.)	1 to 2 drachms (4–8 Gm.).
Liquor Potassii Citratis (8 per cent.)	½ to 1 fluidounce (15–30 mils).
Potassii Hydroxidum [Caustic Potash]	Not used internally.
Liquor Potassii Hydroxidi (5 per cent.) [Liquor Potassæ]	10 to 20 minims (0.6–1.2 mils).

Physiological Action.—A certain amount of potassium in the blood is requisite to life, but an excessive quantity is injurious and even fatal. The harmful action of potassium is due not merely to the presence of too great a quantity of this ion, but to the disturbance of the proportion between it and calcium; the symptoms of potassium poisoning can be produced by a withdrawal of calcium and *vice versa* can be relieved by the injection of calcium.

An excessive quantity of potassium is depressant to the spinal cord, thereby lessening reflex activity, and reduces the contractility of muscle fiber, especially the unstriped. Because of this latter effect potassium lowers the blood pressure, weakening the force of the heart muscle and causing a dilatation of the arteries. Fatal doses arrest the heart in diastole. When administered by the stomach, however, to healthy animals, it is eliminated so rapidly that enormous doses can be borne without marked failure of the circulation.

The salts of potassium, by virtue of their salt action—at least those in which the base is not combined with a poisonous ion—exercise a marked diuretic effect, increasing, however, not only the water constituent, but also the solid matters of the urine. According to Bird and also Schunck, there is a disproportionate increase in the urea. This has led to the belief, which is probably well founded, that potassium increases the oxidative processes of the body so that the nitrogenous metabolism is more perfect and the products of catabolism represent more complete combustion. It is probable, therefore, that the increase in solid matters which is found in the urine is the result not only of the greater activity of the kidney, but is due, at least in part, to increased formation of nitrogenous waste products.

Therapeutics.—As diuretics, the potassium salts may be employed to maintain the action of the kidneys in those cases of nephritis where there is a failure in the elimination of the solid constituents, and consequent toxæmia. It is to be remembered, however, that, if retained in the system, potassium itself exercises a toxic action, and in these cases must be used with discretion. For the purpose of keeping up the renal excretion potassium is especially useful in the treatment of febrile conditions. As hydragogue diuretics the potassium salts are less useful, because less powerful, than the stimulant diuretics in cases of dropsy in which the kidney is healthy. When, however, the dropsy is due to nephritis on account of the comparative absence of irritation of the kidney, they are frequently of much service.

The salts of potassium have long enjoyed a high repute in the treatment of various types of rheumatism, especially in acute articular rheumatism. Their value in this condition is due (1) to the increased diuresis and consequent hastening of the elimination of the toxic substances from the blood; (2) to their effects in increasing oxidation, and (3) to their antacid properties correcting the excessive acidity

of the various secretions which is characteristic of rheumatic conditions.

On account of their effects upon metabolism, potash salts have also been used in various forms of hepatic disorders, such as torpor of the liver and catarrhal jaundice.

Administration.—Where we are seeking for the action of the potassium ion it is essential that it be not combined with a toxic radical. For the latter reason the nitrate and chlorate which were formerly used are greatly inferior to the vegetable salts. The chloride, on account of its greater diffusibility, is far less diuretic in its action than the acetate or citrate. The carbonate and bicarbonate will be changed in the stomach into a chloride, and therefore are not efficient as systemic antacids, unless sufficient dose is given to neutralize the acidity of the stomach, in which case they are liable to interfere with digestion. The acetate and the citrate undergo oxidation in the body and are eliminated as carbonates, thereby rendering the secretions, especially the urine, alkaline. Because they are neutral salts and non-irritant they are less likely to upset the stomach than the carbonates. For these reasons, whenever it is desired to exercise purely a potassium effect, preference should be given to one of these vegetable salts. The citrate, although generally more acceptable to the palate, is less easily absorbed from the intestinal tract and frequently exercises a laxative action rather than a diuretic effect. Especially is this true of the effervescent potassium citrate of the U. S. Pharmacopœia, which contains also sodium tartrate. The dose of either the acetate or citrate is 15 to 30 grains at intervals of two or three hours. In the case of rheumatic fever the potassium salt should be pushed until the urine becomes alkaline. If the solution of these salts is rendered slightly acid by the addition of lemon juice or citric acid they are much more acceptable to the palate.

By virtue of their salt action the potassium salts are also useful as expectorants and diaphoretics. These actions, however, will be considered elsewhere.

The bitartrate, or cream of tartar, has been supposed to exercise a direct stimulant influence upon the kidney, and has been, therefore, very widely used in the various conditions of failing excretion. It is improbable, however, that this substance has any effect upon the system which cannot be attributed either to its potassium ion or to its salt action. As the tartrates are less rapidly absorbed from the intestines, the cream of tartar is even more liable than the citrate to act as a cathartic, and is consequently inferior as a diuretic.

LITHIUM.

The lithium ion is similar in its effects to potassium, but less powerful. In sufficient quantity, however, it is like the potassium, depressing to the heart and to the central nervous system.

Official Preparations:

Lithii bromidum ..... 10 to 20 grains (0.7–1.5 Gm.).
Lithii carbonas ..... 5 to 15 grains (0.3–1.0 Gm.).

Lithium was introduced by Garrod, in 1861, as a remedy for gout, on the grounds that, uric acid being soluble in the presence of lithium salts, the administration of these would prevent the uratic deposits in the joints. But lithium acts as a solvent for uric acid only when present in relatively large amounts, and it has been shown that even in fatally large doses it does not exercise any such effect in the blood. Moreover, there is no convincing clinical evidence that lithium is any more valuable in the treatment of gouty disorders than potassium. The extraordinary vogue which it has enjoyed has been largely due to the so-called lithia waters. These, however, contain only merely spectroscopic traces of lithium, and whatever therapeutic benefit may have followed their use in gout, gravel, or nephritis is to be ascribed to the water rather than to their saline content.

Lithium is useful medicine purely for its salt action, but, as it is somewhat more diffusible than potassium, it is less potent as a diuretic. In its general physiological properties it is very similar to, although less powerful than, potassium.

SALINE DIURETICS.

Edsall ..... Contrib. from Pepper Clin. Lab., 1900, 368.
Magnus ..... A.E.P.P., 1901, xlv, 23.
Asher ..... Th. M., 1908, xxii.
Pauli ..... Verhandl. d. Cong. f. Inner. Med.
Sollmann ..... A.J.P., 1903, ix, 454.

POTASSIUM.

Astalfoni ..... A.I.P., 1903, xi.
Basham ..... Prac., 1870, v.
Dogiel ..... C.M.W., 1892.
Mathison ..... J.P., 1911, xlii, 471.
Ringer and Murrell ..... J.P., i, 88.
Wood (Lithium) ..... J.A.M.A., 1916, lxvi, 1069.

STIMULATING DIURETICS.

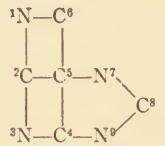
Among the drugs which increase the flow of urine by acting directly upon the renal epithelium, mercury and those which belong to the digitalis series are considered elsewhere.

Almost any substance which is locally irritant and capable of absorption may, under proper conditions, increase the flow of urine. With many of the local irritants, however, the border-line between stimulation with increase of function and irritation with lessening secretion is so narrow that their use for therapeutic purposes is not to be recommended. Probably the least irritant, and therefore the most generally useful, of this group of drugs are the derivatives of xanthin.

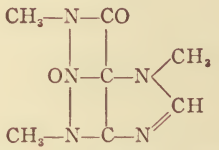
XANTHIN GROUP.

Among the products of nitrogenous metabolism are several substances which may be regarded as derivatives of purin, the most prominent of these bodies being uric acid, which is a trioxy-purin. Another purin derivative which occurs naturally in the excretions is the substance xanthin, which is dioxy-purin. Similar products seem to be formed as the result of metabolic activity in plants as well as animals, for we find in the vegetable kingdom a large number of plants containing bodies allied to xanthin. These are generally methyl derivatives of xanthin. For instance, the longest known and the most important from a medical standpoint of these bodies is caffeine, which is a trimethyl-xanthin.

The base of the group of compounds is the following atom-complex; as it is evident that side groups may be attached at different positions, this nucleus is usually numbered as in the attached formula to indicate the position of these side chains.



The basis of the purin derivatives.



Caffeine: the 1, 3,7 trimethyl-dioxy-purin.

Of the considerable number of derivatives of xanthin which occur naturally or have been prepared synthetically, there are three used to a considerable extent in medicine. These are: two dimethyl-xanthins, theobromine and theophylline, and a trimethyl-xanthin, caffeine.

CAFFEINE.

Materia Medica.—Caffeine is the active principle of a large number of plants which are used in various parts of the world for the purpose of making beverages. Originally discovered in the coffee bean, it is now known to be the active ingredient of tea, of kola nut (from *Sterculia acuminata*), of maté (from *Ilex paraguensis*), of Yaupon or holly tea (from *Ilex cassine*), and of guarana (from *Paullinia cupana*). The last named is the only crude caffeine drug recognized by the U. S. Pharmacopœia.

Coffee is the seed of the *Coffea arabica,* a small tree which is native in tropical Africa, but is cultivated in many parts of the tropical world, the bulk of the supply for this country coming from Brazil. The coffee beans contain from 1 to 2 per cent. of caffeine. Tea is the dry leaves of an evergreen shrub (*Thea chinensis*) native in China and cultivated in various parts of Asia. These leaves contain from 1 to 5, generally about 3 per cent. of an alkaloid which was formerly known as theine, but which is identical with caffeine;

indeed, the bulk of the caffeine upon the market is derived from tea leaves; tea leaves also contain traces of a second alkaloid, theophylline.

Guarana, as it occurs in the market, is a dry paste consisting chiefly of the crushed seeds of the *Paullinia cupana,* a climbing shrub found in Brazil. The U. S. Pharmacopœia requires that it shall contain at least 3.5 per cent. of alkaloid.

Caffeine occurs in long, snow-white, silky or feathery, odorless crystals, of a feeble bitter taste. It has a neutral reaction, but unites with acids to form unstable salts. It is soluble, at 77° F., in 45.6 parts of water, 53.2 parts of alcohol, but dissolves readily in the presence of sodium benzoate.

Official Preparations:

Fluidextractum Guaranæ .....1 to 2 fluidrachms (4–8 mils).
Caffeina .....2 to 5 grains (0.16–0.3 Gm.).
Caffeina Citrata (a mixture of equal parts of Caffeine and Citric Acid).....5 to 10 grains (0.3–0.6 Gm.).
Caffeina Citrata Effervescens (2 per cent.)..1 drachm (4 Gm.).
Caffeinæ Sodio-benzoas (50 per cent.).....5 to 10 grains (0.3–0.6 Gm.).

Physiological Action.—Caffeine is absorbed rapidly from the alimentary tract and eliminated through the kidneys, partially unchanged and partly as dimethyl-xanthine and monomethyl-xanthine.

Nervous System.—The increase in mental activity following the use of caffeine * is so well known that scientific proof of the action of the drug upon the brain is hardly needed. However, it has been shown by experimental psychological methods that there is an increase in both the rapidity and accuracy of the purely intellectual processes, such as are required in mathematical calculations or color perceptions. Those forms of cerebral activity, on the other hand, which involve a combination of mental processes with physical coordination are not improved by caffeine. The wakefulness which follows the free use of the drug is further evidence of this action upon the higher centers of the brain.

In both the frog and at least the lower mammalia convulsions are seen after large doses of caffeine, but in the human being they have not been noted in the few cases of caffeine poisoning which have been reported. That these convulsions are of spinal origin is shown by the facts that they occur in the frog after destruction of the brain and that doses not large enough to give rise to convulsions increase the reflex activity. Although, as stated above, convulsions

* Some authorities believe that the cerebral stimulation produced by coffee and tea is due largely to other substances than the caffeine. The researches which have been made upon this subject are, however, so inharmonious as to render positive conclusions doubtful. The following researches will give a key to the literature: Erdman (A.E.P.P., 1902, vol. 48), E. T. Reichert (*Med. News,* 1890, vol. 56), Binz (C.I.M., 1900, vol. 21), Archangeleski (A.I.P.T., 1900, vol. 75), Geiser (A.E.P.P., liii, p. 112).

have not been recorded in human beings, that the drug is stimulating to the spinal cord of man, as well as the lower animals, is shown by the increase in the activity of the knee-jerk after the administration of caffeine.

The peripheral nerves are not affected by any dose of caffeine which can be given internally, but it is said that concentrated solutions applied locally to the sensory nerves will destroy their conductivity.

The stimulant action of caffeine on the central nervous system is shown not only in its effect upon the brain, but also upon the motor side of the spinal cord.

The stimulation of the medulla is shown chiefly in the increase of the respiratory activity. Although certain investigators believe that caffeine exercises a stimulating effect upon the vasomotor centers,

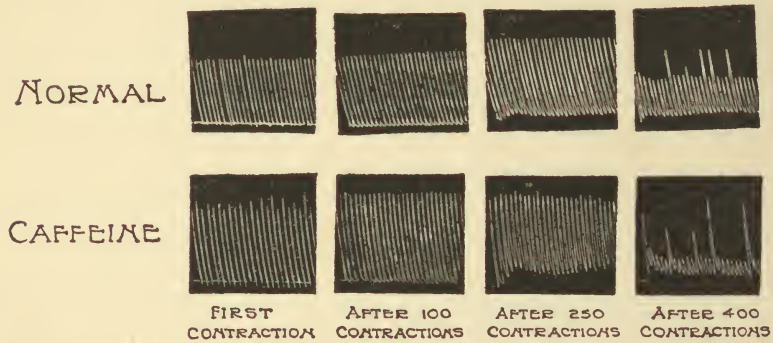


FIG. 2.—The effects of caffeine on voluntary muscle. The two tracings are from the two gastrocnemii of a frog. The muscle which recorded the upper one was kept in a physiological salt solution, the lower one in a dilute solution of caffeine. Note how much larger the contractions of the caffeinized muscle are at the beginning of the experiment. Although they grow smaller now after four or five hundred contractions, the caffeinized muscle does a greater total amount of work before exhaustion.

it is extremely slight, for the small amount of rise in the blood-pressure produced by caffeine is not prevented by the destruction of the medulla.

Muscles.—The action of caffeine upon voluntary muscles is well marked. In moderate quantity it increases the force of the muscular contraction so that the same strength of electrical irritation of the muscles causes a greater contraction. In larger quantity the muscle is reduced in its contractile power, and, in certain species of frogs, is eventually thrown into a condition resembling that of postmortem rigidity. While it is probably possible to cause this peculiar stiffness in all forms of voluntary muscle by the direct local application of caffeine, it is only in certain species of frog that it is brought about by relatively small doses; thus, in the *Rana temporaria* the convulsant action of the drug may be hidden by the effects upon the muscle substance.

A question of much practical importance, especially in view of the universal consumption of the caffeinic beverages, is whether this increase in the muscular power is at the expense of its total energy;

in other words, whether the temporary stimulation is followed by a compensatory depression.

The experience of the use of caffeine-containing substances where large bodies of men are exposed to much physical exertion, as, for instance, in an army on the march, has universally been that more work can be accomplished with the use of some form of caffeine than without it. These results have been scientifically confirmed by the work of Hoch and Kraepelin and others with the ergograph. Both of these forms of testimony, however, may be objected to as not excluding the possibility of the increased physical labor accomplished being due to the heightened activity of the nerve-centers.

In experiments performed by the author, however, with the isolated muscle of the frog, it was found that the total amount of work which could be performed before the muscle becomes exhausted was generally increased by caffeine. It would seem, therefore, that not only does the drug increase the excitability of voluntary muscle, but also, in some way, enables it to work more economically.

Circulation.—There has been much misconception as to the action of caffeine upon the circulation, due largely to the fact that most of the early experiments were made with toxic doses and in part to the fact that the actions of the drug upon various portions of the circulatory apparatus are antagonistic. Therapeutic doses produce but little visible change, perhaps some slowing of the pulse and an insignificant rise in the pressure. After large doses the pulse-rate becomes more rapid than normal, but the blood-pressure is not consistently affected. Toxic doses greatly accelerate the heart and lower the blood-pressure.

Despite the absence of gross changes in the blood-pressure after therapeutic doses of caffeine, the drug affects nearly all the circulatory functions, but, as many of these changes are mutually antagonistic, after small quantities the visible effects are slight. Thus the isolated heart is always increased in the frequency of its contractions, probably through an action directly upon the muscle, but at the same time therapeutic quantities excite the cardio-inhibitory center, so that in normal man the result of small doses is either no change in the rapidity of the pulse or a slight slowing. Both the extent and vigor of the cardiac contractions are increased, at least by therapeutic doses, although after toxic quantities the output of the heart may be diminished. The reason that the blood-pressure is not elevated is that there is at the same time a dilatation of the peripheral blood-vessels which, according to Sollman and Pilcher, is due to an action directly upon the arterial muscles. Confirming this view of cardiac stimulation and vascular relaxation are the observations of Means and Newburg, who found that in normal men the rapidity of blood flow was distinctly increased.

Kidney.—The increase in the flow of urine caused by caffeine is sometimes extraordinary. Although the principal effect of the drug is upon the volume of the urine, there is also an increase in both the

total amount of solids and in the amount of nitrogen excreted; in other words, while the quantity of all the urinary elements is greater, the increase in the amount of water is disproportionately large. The manner in which caffeine produces this diuresis is not definitely determined. It has been shown that under the influence of caffeine the renal vessels are markedly dilated and that usually the diuresis runs more or less parallel both chronologically and quantitatively to the vascular dilatation. Many authors therefore maintain that the increase in the quantity of urine is simply the result of the increased flow of

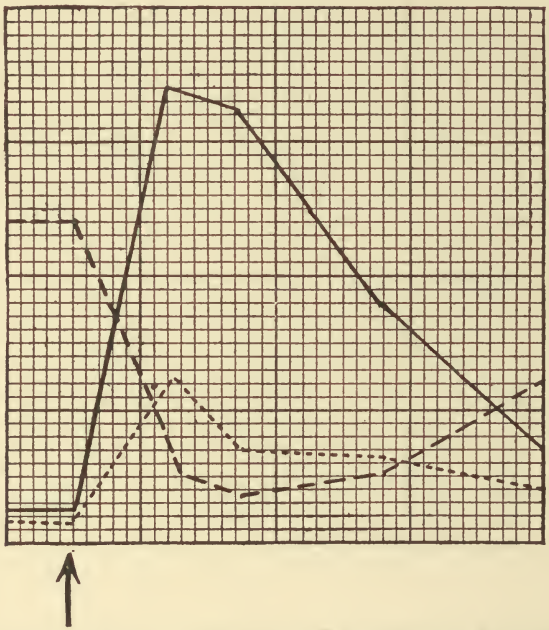


FIG. 3.—The diuretic action of caffeine. The solid line represents the volume of the urine; the broken line the percentage of nitrogenous solids, and the dotted line the total quantity of nitrogen. The arrow shows the point at which the caffeine was injected. Although the percentage of solid matters is diminished, the increase in the volume of the urine was so great that the quantity of solids was increased. (After Von Schroder.)

blood through the kidneys. The evidence to-day, however, is very strong that the action of caffeine upon the kidney is due to direct stimulation of the renal epithelium. In the first place, while there is generally more or less parallelism between the dilatation of the renal artery and the increase in the flow of urine, this relationship is by no means a constant one, and Richards and Plant have been able to demonstrate a diuretic effect upon the artificially perfused kidney with a constant rate of blood flow. Moreover, there is an increased consumption of oxygen by the renal cells. The author, therefore, is inclined to the opinion that the diuresis is due to a direct stimulant action, and the increased flow of blood the result, not the cause, of the increased function.

Metabolism.—The enormous use by mankind of substances containing caffeine has led to the belief that it exercises an influence upon the nutritive processes of the body. The results of the elaborate and repeated investigations seem, to the author, to show that the drug neither increases nor diminishes bodily catabolism as measured by nitrogenous elimination.

In the lower animals a marked elevation of the temperature has been observed after the use of large doses of caffeine. Binz believes that this increase in temperature is due to the increase of muscle tone and consequent greater formation of heat.

Therapeutics.—Caffeine has been used as a stimulant to the kidney, respiration, and circulation, and also for the relief of certain cases of neuralgia. Its effects as a cerebral stimulant, while powerful, are rarely of much therapeutic interest.

As a circulatory stimulant caffeine has been greatly overestimated. Its immediate effects upon blood-pressure are so slight that in cases of acute circulatory failure, such as surgical shock or in the later stages of infectious fevers, it is of relatively little value. It has also been largely used in the treatment of chronic heart weakness, especially depending on valvular lesions. While sometimes of adjuvant service in this condition, it is greatly inferior to the drugs of the digitalis group.

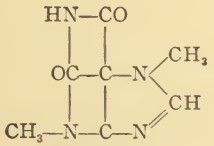
As a respiratory stimulant caffeine is of service, especially in cases of narcotic poisoning, in which its tendency to produce wakefulness enhances its value as a stimulant to the respiratory center.

How caffeine relieves the pain of neuralgic headache we have no idea, but empirically it has shown itself of service in certain cases of migraine and other forms of headache, especially in combination with other analgesics.

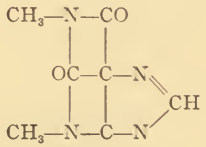
A most important use of caffeine is for its influence upon the kidney, but even here it is being displaced by the other xanthin diuretics. It is, however, largely used in cases of dropsy associated with heart weakness. Its effects upon the kidney are precisely similar in kind although not so great in degree as those of theobromine. (See page 40.)

THEOBROMINE.

There are two dimethyl-xanthins used in medicine, theobromine and theophylline. These differ chemically in the positions of their methyl radicles, as shown in the following formulæ:



Theobromine.



Theophylline.

Materia Medica.—Theobromine is found in the chocolate bean. The chocolate tree (*Theobroma cacao*) is a large, handsome tree, native in Central and South America, cultivated in various parts of the tropics. The fruit is a large, pulpy, oblong berry, six or eight inches in length, in which are imbedded numerous seeds about the size of almonds. These seeds, which are the only part of the plant used, are commonly, but incorrectly, known as chocolate "nuts." From them are prepared a number of popular confections and beverages, known variously as chocolate, cocoa, etc. They contain about fifty per cent. of a solid fat (*Oleum theobromatis*), two to four per cent. of theobromine, and also traces of caffeine.

Theobromine is almost completely insoluble in water, but becomes soluble in the presence of certain salts, notably sodium salicylate and sodium acetate, and is generally used in combination with one or the other of these salts.

Theophylline is found in small quantities in tea leaves, but the proportion is so insignificant that it was not available as a commercial product until its synthetic production under the trade name of theocin. It is soluble in about 180 times its weight of water, but, like theobromine, its solubility is increased by various salts.

Neither of these alkaloids is recognized at present by the United States Pharmacopœia. The following preparations, however, are those most frequently employed: Theobromine, theobromine and sodium salicylate (diuretin), theobromine and sodium acetate (agurin), theophylline (theocin), theophylline sodium acetate (soluble theocin). Dose of either theophylline or theobromine, five grains (0.3 Gm.).

Physiological Action.—These two alkaloids appear to be almost identical in their effects upon the system. In a general way their action is similar to that of caffeine, but they differ from this alkaloid in that their effects upon the central nervous system and upon the circulation are relatively much less marked. The statement, however, which is sometimes made that theobromine is without influence upon these portions of the body is incorrect, although after doses which are ordinarily employed, unless in persons who are unusually susceptible to the drug, no effects of stimulation of the circulation nor of the brain are observable. Since they are relatively less potent in their effects upon the central nervous system, it is evident that they must be relatively more powerful in the other actions characteristic of the group; namely, the peculiar effect on muscle-tissue and the stimulant action upon the kidneys.

Therapeutic Uses.—In cases of kidney insufficiency, especially when there is a failure to excrete water, and consequent occurrence of œdema, the diuretics of the xanthin group are among the most valuable remedies which we possess. Although, as noted previously, the percentage of solids in the urine is less than normal after the exhibition of these drugs, yet the total quantity of the urine is so greatly increased that the amount of solids eliminated in a given time

is larger than normal. The question as to whether these drugs act by stimulating the epithelium or simply by dilating the blood-vessels of the kidney—in other words, whether their action is likely to be attended with irritation in inflamed conditions of this organ—cannot at present be positively answered, but the author inclines to the view that it is the result of a direct stimulation of the kidney. Although we are not able to say that they are not irritant to the inflamed kidney, they are certainly much less so in proportion to their diuretic power than most of our stimulant diuretics, and are therefore, perhaps, probably the least harmful drugs to use in cases of nephritis. In certain cases, however, of renal diseases they may fail entirely to act. According to the experiments of Schlayer and Hedinger, it would seem that the results of their use depend chiefly upon the character of the lesion in the kidney; these authors found that so long as the glomeruli were intact, even although there were very extensive alterations in the tubules, caffeine exercised a profound diuretic influence, but that after involvement of the glomeruli its diuretic power was greatly diminished, and, if the morbid condition be at all advanced, completely lacking.

When a purely diuretic effect is desired the preference should generally be given to theobromine or theophylline, on account of the liability of caffeine, if given in full dose, to produce wakefulness. They are, however, more likely to disturb the stomach than is caffeine, and the latter is, therefore, at times, preferable as a stimulant to the kidneys. When there is weakness of the circulation associated with renal failure the stimulant action of caffeine upon the heart is often of distinct advantage.

In my own experience, theophylline has proven more certain and powerful in its diuretic effect than either theobromine or caffeine, but some authors believe that it is also more distinctly irritant to the kidney. A peculiar fact which has been noted concerning the action of theophylline is that when its use is continued for a period of several days it loses its power; indeed, the quantity of urine may be diminished below the normal. The explanation of this phenomenon is at present not clear, but the practical conclusion is that this drug should not be administered for more than a few days without interruption; if the administration is interrupted every four or five days for twenty-four to forty-eight hours it can be used with benefit for long periods of time.

OIL OF JUNIPER.

Materia Medica.—The berries of the common juniper (*Juniperus communis*), an evergreen shrub found in both North America and Europe, are a dark purplish color and about the size of a large pea. By distillation they yield from 0.5 to 2.5 per cent. of a volatile oil. The oil of juniper is a greenish-yellow liquid with a characteristic odor of juniper and a warm, somewhat terebinthinate, taste.

Official Preparations:

Oleum Juniperi.....1 to 10 minims (0.3–0.6 mil).
Spiritus Juniperi (5 per cent.).....½ to 1 fluidrachm (2–4 mils).
Spiritus Juniperi Compositus (4 per cent.)..2 to 4 fluidrachms (8–15 mils).

Physiological Action.—Juniper is gently stimulant and cordial to the stomach. Upon the kidneys the oil exerts a decided stimulant action, and when freely given is capable of irritating the renal organs above the secreting point, and of producing lessened secretion, strangury, and even suppression of urine. Juniper is largely used as an adjuvant to potassium bitartrate or the alkaline diuretics. On account of its stimulant local influence upon the alimentary canal, it renders the cream of tartar far more acceptable to the stomach, and at the same time aids its diuretic action. Sometimes juniper is employed for its stimulant action on the mucous membrane of the genito-urinary organs in chronic pyelitis and chronic catarrh of the bladder. In the form of the compound spirit or its equivalent, gin, juniper is often useful in the subacute congestion of the kidneys frequently seen in old persons, and characterized by aching in the loins and lessened urinary secretion without more serious symptoms. Its use should be avoided in all active inflammations of the kidney.

CAFFEINE.

Archangeleski .....A.I.P.T., 1900, lxxv.
Baco .....J. de P.P., 1908, x, 32.
Binz .....C.I.M., 1900, xxi.
Erdmann .....A.E.P.P., 1902, xlviii.
Geiser .....A.E.P.P., 1905, liii, 112.
Hollingworth .....Arch. of Psychology, 1912, iii, No. 22.
Kakowski .....A.I.P.T., xvi, 21.
Loewi .....A.E.P.P., 1905, liii, 15.
Means and Newburg .....J.P. & Ex.T., 1915, vii, 449.
Richards and Plant .....J.P. & Ex.T., 1915, vii, 485.
Schlayer and Hedinger .....D.A.K.M., 1908, xci.
Schneider .....Schicksal des Caffeins, Dorpat, 1884.
Sollman and Pilcher .....J.P. & Ex.T., 1911, iii, 19, 609.
Wood, Jr. .....T.G., 1911.

THEOBROMINE.

Bondzynski and Gottlieb .....A.E.P.P., xxvii, 385.
Cohnstein .....A.E.P.P., 1892, xxx.
Farr and Welkin .....A.In.M., 1912, x.
Sabashnikoff .....Thesis, St. Petersburg, 1892.

UVA URSI GROUP.

There is a group of drugs with very feeble diuretic power, but which are used to a large extent in the treatment of inflammatory conditions of the urinary mucous membrance, especially of the bladder. While many of this group of plants which have been recommended in the past

appear to be quite inert, some of them seem to possess feeble therapeutic properties. Their beneficial effects are due in part to volatile oils in them, which have a slight stimulant action upon the kidneys, also in part to antiseptic principles, but probably chiefly to the water with which they are almost invariably administered.

Materia Medica.—*Uva Ursi,* or bearberry, is the leaves of *Arctostaphylos uva ursi,* a trailing evergreen shrub, indigenous to northern maritime Europe and also to our northern coasts as far south as New Jersey. They are from half an inch to an inch in length, wedge shaped, thick, coriaceous, with a smooth, rounded margin. The odor is hay-like, the taste bitterish, astringent, and somewhat sweetish.

The most important principle in *uva ursi* at present known is the glucoside arbutin, of which it contains about 4 per cent. This glucoside is broken up by sulphuric acid into glucose and hydroquinone; a similar decomposition takes place in the body. Hydroquinone ($C_6H_4OH_2$) is an active antiseptic of the phenol series, and it was formerly believed that the hydroquinone formed in the body after the administration of uva ursi exercised an antiseptic influence in the bladder, but Bass finds that hydroquinone, whether administered directly or in the form of arbutin, unites, before elimination, with glycuronic acid and throws serious doubt on the therapeutic efficacy of this drug.

Sabal.—The dried fruit of the saw palmetto (*Serenoa serrulata*) contains a volatile oil, to which it probably owes any therapeutic virtues that it may possess. The saw palmetto is a shrub-like palm indigenous to the South Atlantic coast of the United States. The dose of the crude drug is 15 grains (1 Gm.).

Buchu is the leaves of *Barosma betulina,* a shrub native to Southern Africa. These leaves are an inch or less in length, from three to five lines broad, of various forms, but always notched on the edges, and having a strong, rather rank, yet somewhat aromatic odor, and a warm, bitterish taste. They owe their virtues chiefly to a volatile oil which yields a stearopten known as diosphenol.

Triticum is the dry rhizome of the *Agropyron repens,* a common weed, popularly known as couch grass or quick grass. It appears to contain no substance more active than various gum-like substances, and is probably therapeutically worthless.

Official Preparations:

Fluidextractum Buchu	1 fluidrachm	(4 mils).
Fluidextractum Sabal	15 minims	(1 mil).
Fluidextractum Tritici	2 fluidrachms	(8 mils).
Fluidextractum Uvæ Ursi	1 fluidrachm	(4 mils).

Therapeutic Uses.—These drugs are used chiefly in cases of cystitis and irritable conditions of the bladder; less frequently in pyelitis and urethritis.

DIAPHORETICS.

The same conditions which influence the secretion of urine also affect the secretion of sweat, with the addition that the sweat-glands are also under the control of the central nervous system and drugs may affect their secretion by acting upon the nerve supply; therefore, anything which increases the volume of the blood tends to increase the secretion of sweat, so that just as water acts as a diuretic, it may also act as a diaphoretic, provided that it is directed towards the skin through the aid of external heat. So also do the salines, by attracting water into the blood, increase the sweat as well as the urine. Again, just as drugs which increase the circulation through the kidney increase its activity, so do those drugs which produce a determination of blood to the skin increase the secretion of sweat.

When an agent is capable of acting either as a diuretic or sudorific, the result of its administration will generally be determined by the surrounding temperature, and for this reason, whenever it is desired to produce sweating, external heat should be applied simultaneously with the administration of the drug. We may divide the diaphoretics into three groups:

1. Those which act by virtue of their salt action. The most important of these are potassium citrate and the solution of ammonium acetate commonly known as spirit of Mindererus.

2. Those which act by increasing the circulation through the skin; these may be subdivided as follows: (*a*) Nauseating drugs, such as ipecac, which is the only one of this class used to-day to any large extent, although any emetic drug will produce the same effect; (*b*) agents which profoundly influence the general circulation, as tincture of aconite, and the nitrites, especially the spirits of nitrous ether; (*c*) certain drugs which have a specific action in dilating the vessels of the skin, the most important being alcohol and opium.

3. Those which act directly upon the secreting structures or their nerve supply. Of these the only one of clinical importance is pilocarpine, although there are other drugs similar in effect, pharmacologically.

Sudorifics are used in medicine for the following purposes:

1. *To abort diseases in their formative stage.* Just how a profuse sweating can abort an infectious disease is not manifest, but clinical evidence is very strong that some of the minor infections, such as the condition commonly known as a "cold," can often be cut short in the beginning by a profuse diaphoresis. In the bygone days of the humoralistic pathology this action was explained on the ground that evil humors of the body were expelled with the sweat. Modern writers have changed the wording and say that toxins are eliminated through the glands of the skin, but I must confess that the modern

explanation does not seem to me to be any great advance over that of our grandfathers.

There is also some clinical evidence, although not so strong, that just as diseases may be arrested in their formative stage by a profuse sweating, so in those conditions which terminate with a crisis this may be sometimes precipitated by the use of diaphoretics.

2. *To aid in the elimination of poisonous material.* While it seems to me more than doubtful whether by stimulating the sweat-glands we can increase the elimination of bacterial toxins, there is no doubt that many poisons are eliminated through the skin, and it is probable that the rapidity of their excretion is aided by increasing the activity of the sweat-glands.

That urea may appear in the sweat, under certain conditions, especially when kidney excretion is scanty, has been proven by numerous observers. This being true, it is a fair presumption, and one which has been confirmed abundantly by clinical experience, that the poisons of lithæmia and uræmia may pass out of the body through the glands of the skin.

3. *To evacuate fluid.* For the relief of dropsy the diaphoresis is generally a less powerful measure than free catharsis or diuresis, but as an adjuvant to these measures or in conditions in which the patient cannot stand the more violent methods the diaphoretics are frequently of much service.

4. *To lessen fever.* In mild febrile conditions, where the skin is dry, the encouragement of perspiration tends to keep the fever low through the evaporation of the moisture from the skin. It is possible, also, as mentioned above, that some noxious material may be eliminated through the skin under these circumstances.

PILOCARPUS.

Materia Medica.—Under the name of Pilocarpus, the United States Pharmacopœia recognizes the leaflets of two South American shrubs, the *Pilocarpus jaborandi* and the *Pilocarpus microphyllus.* The leaflets of the former are three to four inches long, oblong or oval in shape, with entire margin and stout petiolules, pellucid, glandular, with prominent veins on both sides. In the small-leaved pilocarpus the leaflets rarely exceed one and one-half inches in length, and the veins are less prominent, and the lateral leaflets are without petiolules. Both of these drugs have a bitterish, somewhat aromatic, salty taste. Their therapeutic activity is due to the presence of pilocarpine, although they appear to contain at least three other alkaloids—jaborine, pilocarpidine, and isopilocarpine. Of these three latter, jaborine appears to act upon the system much like atropine, and is therefore antagonistic to the dominant alkaloids, while pilocarpidine, and probably also isopilocarpine, are similar in their effects to pilocarpine.

Official Preparations:

Fluidextractum Pilocarpi.....½ to 1 fluidrachm (2–4 mils).
Pilocarpinæ Hydrochloridum.....½₂ to ¼ grain (0.005–0.015 Gm.).
Pilocarpinæ Nitras.....½₂ to ¼ grain (0.005–0.015 Gm.).

Physiological Action.—The most important effects of pilocarpine are due to stimulation of certain nerve terminations.

The efferent nerves of the body may be divided into those supplying voluntary muscles, commonly called motor nerves; and those to structures not under direct control of the will, which may be desig-

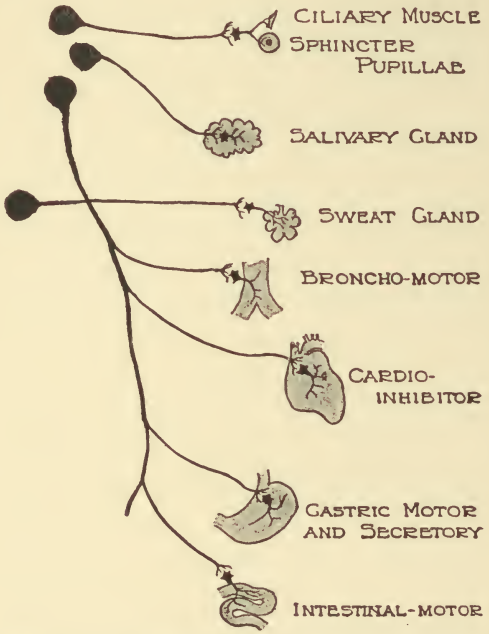


Fig. 4.—Diagram to show the distribution of the important autonomous nerves.

nated as the vegetative nerves, including all the other efferent paths of conduction. The vegetative nerves are of two classes—those which pass through the chain of ganglia immediately in front of the spinal column, constituting the sympathetic system; and those which run directly from the brain or cord to the peripheral ganglia, which have been called the autonomic nerves. We may therefore divide the efferent nerves into three groups: the motor nerves, the sympathetic, and the autonomic. The most important of the last group are three cranial nerves—the oculo-motor, chorda tympani, and pneumogastric—and the pelvic nerve, which arises from the sacral portion of the cord. Pharmacologically, the nerves to the sweat glands appear to belong also to this group. Certain poisons show marked predilection for one or the other

of these groups of nerves; if a drug affects any nerve in one of these groups usually it affects all the nerves in the group. There are some substances which if given in sufficient quantity seem to be capable of acting upon more than one of these groups, but even these drugs generally show a more or less clearly defined selective action on one group.

Since the autonomic nerves supply a large variety of structures and organs of very different function, it follows that the changes produced in the functions of the body by those drugs which act upon autonomic nerves are protean.

A typical example of this group of drugs is found in pilocarpine, which stimulates the peripheral endings of all the autonomic nerves. These include the motor-oculi, the pneumogastric, the secretory fibers of the chorda tympani, the nerves to various other glands, including

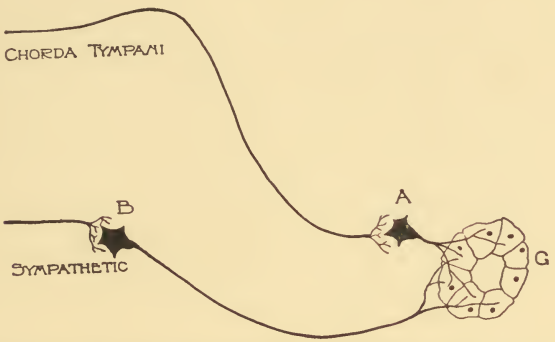


FIG. 5.—Diagram showing the innervation of the submaxillary gland. Pilocarpine increases secretion by stimulating the intraglandular terminations of the chorda tympani nerve.

the sweat, the intestines, the gastric, the lachrymal, etc., and to some unstriped muscle, especially portions of the alimentary tract.

Since pilocarpine excites the above-named organs to excessive function after their nerves have been cut, it is evident that its action is upon some structure peripheral to the nerve-center, but precisely upon what portion of the nerves these drugs act is as yet uncertain. There are certain phenomena which are absolutely inexplicable in view of our present knowledge of physiology. For instance, if the nerve supplying the sphincter muscle of the pupil is cut and a sufficient length of time allowed to elapse to insure degeneration of the peripheral filaments of the nerve beyond the point of section, and then pilocarpine is instilled into the eye, it will contract the pupil. This would seem to show that the action of pilocarpine is directly on the muscle, but if into a normal eye we instil atropine, pilocarpine does not cause contraction of the pupil, and it can be shown that the action of atropine is not upon the muscle of the iris; it is evident that the pilocarpine must have acted upon some nervous structure. But

we have no knowledge of any form of nerve structure which will survive the separation for a long period of time from its controlling center. We are therefore unable to state precisely what portion of the motor apparatus is affected by these drugs, and we content ourselves by saying it is the peripheral nerve-endings.*

Secretion.—The most prominent effect of the ingestion of a therapeutic dose of pilocarpine is an increase in the secretory activity of nearly all the glands of the body, especially of the salivary and sweat-glands. That there is a true exaltation of glandular function is shown by the fact that the solid matters of the saliva, as well as the fluid, are increased in quantity. As this effect is not abolished by section of the nerve, it must be regarded as due to an action upon some structure within the gland itself; but, as the effect is put aside by atropine, it cannot be upon the secretory epithelium, and, therefore, must be due to an action upon the nerve terminals. The other glands which are affected include the pancreas, the lachrymal and the bronchial glands. The mammary gland appears to have a different type of innervation, and the present evidence tends to show that it is not affected by pilocarpine.

Concerning the effect of this alkaloid upon the kidney there has been in the past some difference of opinion. After large doses of pilocarpine there is a marked decrease in the secretion of urine, which was at one time explained on the supposition that the amount of fluid lost through the skin and saliva was so great as to diminish the volume of the blood. But the recent experiments of Baco and Plumière indicate that it is due to the lowering of the blood-pressure.

The secretion of bile does not appear to be affected.

Involuntary Muscle.—The experiments of Magnus show that pilocarpine causes a marked increase both in the tone and size of the contractions of the intestinal muscles, even after destruction of Auerbach's plexus. Small doses of atropine will relax the increased tone, but not prevent the muscular contractions, although the latter are also set aside by larger doses of atropine. It would seem, therefore, that the action of pilocarpine upon the intestines is an excitation of the peripheral ends of their motor nerves. There is reason to believe that all of the unstriped muscles of the body, except that of the circulation, are similarly affected. Dixon and Brodie have shown that there is partial spasm of the bronchial muscles due to an action upon the peripheral ends of the pulmonary branch of the tenth nerve.

Eye.—The instillation of pilocarpine into the eye causes a contraction of the pupil and a spasm of the muscle of accommodation. Upon just what structure the drug acts to produce these changes is at present uncertain. It is evidently peripheral, because it is not pre-

*Langley (J. P. 1905, xxxiii, p. 374 and 1907, xxxvi, p. 113) believes that the action of this group of drugs is not upon the nerve tissue but upon some receptive substance in the muscle. Similar conclusions concerning the action of muscarine upon the heart have been reached by Minds.

vented by section of the nerves. Since the contraction of the pupil is overcome by atropine, it would seem that it cannot be muscular. On the other hand, Anderson has found that pilocarpine is capable of contracting the pupil after degeneration of the short ciliary nerves, which would seem to preclude an action upon the nerve terminal. The only reasonable explanation available of these somewhat contradictory results is the supposition of a junction between the nerve terminals which is neither muscular nor nervous tissue, to which the name has been applied of neuro-muscular junction.

Circulation.—The characteristic effect of pilocarpine upon the circulation is to produce a marked slowing of the pulse with a fall in the blood-pressure, the latter being caused by the lessened rate of the heart.*

The reduction of the pulse-rate is the result of a stimulation of the intracardiac terminations of the pneumogastric nerve. After toxic doses there appears also to be a depressant effect upon the arterial and cardiac muscles, but the therapeutic dose has no action on the circulation except in altering the pulse-rate.

Therapeutic Uses.—Pilocarpine is the most reliable sudorific drug employed in medicine. Because of the violence and harshness of its action, however, it is usually reserved for those cases where it is desired to sweat profusely, as in the treatment of uræmia. When used incautiously, however, it is capable of producing serious or even fatal pulmonary œdema. This fact is probably due to a combination of increased bronchial secretion, partial spasm of the bronchial muscles, and weakening of the heart through stimulation or inhibition. In the author's opinion, however, the danger from this drug is usually greatly exaggerated. If its action be directed toward the skin by the use of the hot-pack the effect on other glands will be greatly diminished. On the other hand, the doses which are often recommended are needlessly and dangerously large. Only extreme conditions can justify a larger quantity than one-eighth of a grain hypodermically, and it should always be employed in connection with some form of external heat.

As a local remedy pilocarpine is largely employed for the purpose of contracting the pupil in glaucoma, and various other diseases of the eye.

Pilocarpine is also occasionally used as a stimulant to peristalsis, especially of the bowels, but for this purpose it is generally inferior to physostigmine. It has also been popularly attributed with the power of stimulating the growth of hair, but this is probably incorrect.

It may be well to call attention to the fact that if for any reason there occurs excessive action or undesirable effects from pilocarpine, the symptoms may generally be readily controlled by the administration of its physiological antagonist—atropine.

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* For some unknown reason the therapeutic dose produces frequently in man an increase instead of a decrease in the rate of the pulse.

MUSCARINE.

This alkaloid, which is found in a poisonous toadstool, *Agaricus muscaris,* closely resembles pilocarpine in all its physiological actions. It causes marked slowing of the pulse, contraction of the pupil, increase in secretion, and bronchial spasm, by stimulation of the nerve terminals. The cause of death from this substance appears to be largely the result of the excessive excitation of the intracardiac inhibitory mechanism.

It is not used in medicine, but is of some interest from a toxicological standpoint. Atropine is a complete physiological antidote.

PILOCARPINE.

Anderson ..... J.P., 1905, xxxiii.
Baco and Plumière ..... J.deP.P., 1908, x, 32.
Ewing ..... J.P. and Ex.T., 1911, iii, 1.
Dixon and Brodie ..... J.P., 1903, xxix.
Gottlieb ..... A.E.P.P., 1894, xxxiii, 261.
Harnack ..... A.E.P.P., xx, 439.
Magnus ..... A.G.P., 1905, cviii, 1.
Ringer ..... Pract., xvii, 401; xxvi, 12.

MUSCARINE.

Cushny ..... A.E.P.P., 1893, xxxi, 431.
Mines ..... J.P. and Ex.T., 1914, v, 425.
Schmiedeberg and Harnack ..... A.E.P.P., 1876, vi, 101.
Straub ..... A.G.P., 1907, cxix, 127.

EXPECTORANTS.

Expectorants, in the narrower sense of the word, are drugs which are used for the purpose of increasing secretion of the bronchial mucous membrane, but, as ordinarily employed, the term refers to any substance which is used for its effects in inflammatory conditions of the bronchi, whether the amount of secretion is increased or not. For the purpose of study, the expectorants may be divided into two groups, those which tend towards relaxation of the bronchial blood-vessels and increase of secretion—the so-called sedative or nauseating expectorants—and those which, by virtue of a local stimulating action upon the bronchial mucous membranes, tend to restore tone to dilated blood-vessels. The first group are to be chosen in the early stages of an acute bronchitis, before secretion is established, while the "cough is tight"; the second group are more useful in chronic bronchitis or in the advanced stages of an acute condition.

Of course, it must be understood that the division which has been made is arbitrary, and that very frequently there are conditions in which expectorants of one group may well be combined in one prescription with those of another group.

NAUSEATING EXPECTORANTS.

One of the effects of nausea is an increase in bronchial secretions, the result of the general relaxation which takes place, and therefore

any nauseating emetic may act as an expectorant. Those which are used practically for this purpose include lobelia, tartar emetic, ipecacuanha, potassium citrate, apomorphine, and the saponin drugs. With the exception of the last these have other important uses and are considered elsewhere in this work.

Saponins.—Under this term have been included a number of glucosidal bodies whose chemical relationship has not yet been clearly determined, but which are certainly closely allied in their chemical as well as their physiological properties. Some of them are active poisons, while others are comparatively feeble. The term "saponin" is given them because, like soap, they are capable of emulsifying fatty substances, and they are hence frequently employed as cleansing agents. This group of principles is very widely distributed throughout the vegetable kingdom, Kobert giving a list of 140 plants which contain principles of the saponin class.

The Sapotoxins—a term sometimes applied to designate poisonous members of the saponin group—are local irritants, and when taken into the alimentary tract cause violent vomiting and purging, or, if applied to the skin, are capable of setting up a dermatitis. They are poisonous to all forms of protoplasm with which they come in contact, diminishing the functional activity of muscles and nerves exposed to their solutions. Their most striking property, however, is that of causing solution of the red blood-cells, some of them being so powerfully hæmolytic that one part with 100,000 is sufficient to cause laking of the blood. It should be noted, however, that most of the sapotoxins appear to be non-absorbable by mucous membranes, and that in poisoning by them, therefore, the systemic symptoms are lacking, the evidences being simply of gastro-intestinal irritation.

The sapotoxins, by virtue of their local irritant action upon the stomach, produce vomiting or, in smaller doses, nausea. As a result of this nauseating effect there is an increase in both the bronchial secretions and the sweat. The plants, therefore, which contain saponin have been largely used as nauseating expectorants, to a lesser extent as diaphoretics. Whether or not saponins possess any action upon the bronchial mucosa aside from their nauseating action is at present a matter of difference of opinion, but my own belief is that all of their virtues in bronchitis may be attributed to their effects on the stomach.

There are a considerable number of plants which contain small quantities of saponins, but not enough to play any part in their therapeutic action. *Quillaja,* or soap-bark, which was formerly official, is used largely as a detergent, but scarcely at all as a medicine. The only drug at present recognized by the Pharmacopœia which is valuable for its saponin action is senega. This is the root of the indigenous *Polygala senega,* known popularly as snake root.

Official Preparations:

Fluidextractum Senegæ.....10 to 15 minims (0.6–1 mil).
Syrupus Senegæ (20 per cent.).....1 fluidrachm (4 mils).

STIMULATING EXPECTORANTS.

The term "stimulating expectorants" is an unfortunate one, as it suggests that this group of drugs excites a bronchial secretion. Their action, however, seems to be due to a local irritant effect upon mucous membrane of the bronchi. When the latter is the seat of a passive congestion this action tends to restore tone to the dilated blood-vessels; the secretion, if excessive, will generally be diminished.

The stimulating expectorants considered elsewhere in this work include creosote and its derivatives and certain volatile oils, notably eucalyptus.

TURPENTINE.

Turpentine.—The word turpentine is applied to the exudation obtained by wounding various coniferous trees, especially different species of pine and fir. These exudates are mixtures of volatile oil with resinous material. The turpentine most commonly encountered in the United States is that obtained from the *Pinus palustris,* or yellow pine. Turpentine differs more or less in both its physical properties and chemical composition, according to the sources from which it is derived. The American turpentine, which was formerly official under the name of *Terebinthina,* occurs in yellowish, opaque masses, practically insoluble in water, but completely soluble in alcohol. When subjected to distillation it separates into a volatile oil and a resin, known popularly as rosin or colophony, both of which are recognized by the Pharmacopœia. The so-called Canada turpentine or Canada balsam is the product of the *Abies balsamea,* or American silver fir. This is rarely employed medicinally. It is of importance in microscopy as a cement for glass.

The *oil of turpentine* (frequently but incorrectly called "spirits of turpentine") is a colorless or slightly yellowish, highly inflammable liquid, immiscible with water, but soluble in 5 parts of alcohol, and miscible in all proportions with the fixed oils. When pure it consists of a mixture of various terpenes ($C_{10}H_{16}$), of which the most important is the dextro-pinene. By heating with hydrochloric acid it is converted into a red liquid and a white crystalline substance, pinene hydrochloride, which, from its resemblance to camphor, has received the name of *artificial camphor.* When exposed to the air turpentine absorbs oxygen, part of which appears to unite with the terpene, but some is converted into ozone and held in solution, so that the oil of turpentine after its exposure to the air becomes an active oxidizing agent. When intended for internal use the oil of turpentine is purified by washing it with a solution of sodium hydroxide and redistilling.

Terebene is a clear, colorless liquid, insoluble in water, isomeric with terpene, and of a peculiar odor, somewhat resembling that of freshly sawed pine wood. It is prepared by the action of sulphuric acid upon oil of turpentine.

Terpin hydrate is made by acting upon oil of turpentine with nitric acid. It occurs in the form of colorless and nearly odorless crystals with a slightly bitter taste, almost soluble in water, but soluble in 10 parts of alcohol.

Official Preparations:

Oleum Terebinthinæ	Not used internally.
Oleum Terebinthinæ Rectificatum	5 to 15 minims (0.3–1.0 mil).
Emulsum Olei Terebinthinæ (15 per cent.)	½ to 1 fluidrachm (2–4 mils).
Linimentum Terebinthinæ (35 per cent.)	External use only.
Terebenum	3 to 5 minims (0.2–0.3 mil).
Terpini Hydras	2 to 3 grains (0.15–0.2 Gm.).

The following are the preparations of rosin:

Ceratum Resinæ [Basilicon Ointment]	External use only.
Ceratum Cantharidis	External use only.
Linimentum Terebinthinæ	External use only.

Physiological Action.—Locally, oil of turpentine is a powerful irritant, causing in a very short time inflammation in any tissue with which it comes in contact. Oil of turpentine is a feeble disinfectant, but appears to be especially antagonistic to the *Bacillus typhosus*.

When taken by a healthy person, in moderate doses, it produces a sense of warmth in the stomach, soon followed by exhilaration, and, if the amount be sufficient, giddiness and even a species of intoxication. The pulse is increased in force and frequency. The turpentine escapes from the body through the lungs and kidneys, imparting its own odor to the breath and that of violets to the urine.

Concerning the general effects of turpentine upon the system, there has been in the past considerable divergence in statements, but this appears to be due to the fact that the European substance known as oil of turpentine differs from that in the American markets. The American oil of turpentine has, in toxic doses, a depressant action upon the sensory side of the nervous system, and also upon the heart.

Therapeutic Uses.—Oil of turpentine is used for four purposes in medicine: (1) As a counterirritant, (2) as a carminative, (3) as a diuretic, and (4) as an expectorant.

As a counterirritant oil of turpentine may be used either in the form of a liniment or of the turpentine stupe. The latter may be made in one of several ways, according to the severity of effect which is desired. The mildest form of stupe is made by wringing out a piece of flannel in hot water and sprinkling with a few drops of turpentine and applying to the body; a more decided effect can be obtained by wringing out the flannel first in hot water and then afterwards in turpentine, while the most active stupe is one which is made by wringing out a piece of dry flannel in turpentine previously warmed by setting in a pan of hot water. The powerful counterirritant effect

which is obtained by the stupe is due to the combination of the effect of the heat and the local irritant action of the turpentine. It should be left in place for from fifteen minutes to half an hour. As a liniment turpentine may be used in the strength of 25 to 50 per cent., generally mixed with cotton-seed oil.

As a carminative, oil of turpentine is one of the most valuable remedies we possess for the relief of flatulence. It is especially useful in the treatment of typhoid fever. There are two conditions or stages in this disease in which it is especially useful—indeed, is of incalculable service. About the end of the second week the tongue sometimes becomes very dry, red, chapped, perhaps coated in the center with a brownish fur, and at the same time marked meteorism develops. Five to ten minims (0.6 C.c.) of turpentine every three or four hours will in the majority of cases remove the bad symptoms noted. That the action of the oil is largely a local one is shown not only by the arguments of the introducer of the practice, George B. Wood, but also by the value of the same treatment when diarrhœa persists after the acute stage of the fever has passed. When convalescence is protracted, when there is a constant tendency to the recurrence of diarrhœa—when, in other words, the ulcers of Peyer's patches are slow to heal—turpentine acts almost as a specific. These clinical results have received scientific confirmation in the work of Theo. Omelchenko, who finds that the bacillus of typhoid fever will not develop in air containing diluted vapor of turpentine, and dies when the atmosphere is saturated with the vapor.

Under this head may also be included the use of oil of turpentine as an addition to enemata. From a teaspoonful to a tablespoonful added to a pint of soap-suds forms the so-called "compound enema," which is much more active than the simple injection and especially useful in causing expulsion of flatus.

As a diuretic, turpentine is to-day employed but rarely, but is occasionally useful for its local stimulant action upon the mucous membrane of the urinary tract in chronic pyelitis, cystitis, and gleet.

As a stimulating expectorant in cases of chronic bronchitis, especially where there is free expectoration, oil of turpentine is a very valuable remedy, although preference is generally given to one of its derivatives, especially terebene. Terpin hydrate, although widely used, is of much inferior value.

Administration.—The oil of turpentine should be always administered in the form of an emulsion, because of the lesser liability to irritate the stomach. The practice of giving it enclosed in capsules is not to be recommended. Terebene may be administered in emulsion, or simply dropped in a spoonful of sugar, although the latter method is liable to give rise to gastric irritation. A method of administration which I have found useful is to mix the terebene with an equal weight of powdered licorice root and enclose it in a gelatine capsule. This mixture is less likely to irritate the stomach than

if the substance is given undiluted. Terpin hydrate is generally administered dissolved in an alcoholic elixir.

Oil of Pine Needles.—Under the title of *Oleum Pini Pumilionis* the U. S. Pharmacopœia recognizes the oil distilled from the needles of the dwarf pine or mountain pine from central Europe. This consists chiefly of lævo-pinene, but has the pleasant, pine-like odor of bornyl acetate. It may be used for the same purposes as oil of turpentine, but is more commonly employed for inhalation in the treatment of bronchitis. For this purpose 8 or 10 drops may be added to a pint of boiling hot water and the vapors inspired.

TAR.

Materia Medica.—Tar is a black, semi-liquid substance obtained by the destructive distillation of various species of pine. That used in this country is obtained almost exclusively from the *Pinus palustris*. Tar has a sharp, aromatic, and somewhat bitter taste. It is a very complex substance of not constant composition, containing phenol and a number of allied bodies, including cresol, guaiacol, and creosol. It probably also contains more or less oil of turpentine.

Official Preparations:

Oleum Picis Liquidæ .....3 to 5 minims (0.2–0.3 mil).
Syrupus Picis Liquidæ (5 per cent.).....1 to 2 fluidrachms (4–8 mils).
Unguentum Picis Liquidæ (50 per cent.).....External use.

Therapeutic Uses.—Tar, especially in the form of the syrup, offers an elegant and efficient remedy for subacute and milder types of chronic bronchitis. In my own experience, although less active than creosote, it is better borne by the stomach and is much more agreeable to the palate.

Locally it is much employed in the treatment of chronic inflammations of the skin as a stimulant antiseptic application.

GRINDELIA.

This is the leaves and flowering tops of *Grindelia camporum* and of *Grindelia squarrosa,* plants inhabiting the extreme western portions of North America. In commerce the whole herb, including the stems, roots, and floral heads, is sold. The taste is warmish, peculiar, and very persistent. The presence of a crystalline alkaloid in grindelia has been asserted by several investigators, but at present it seems probable that its activity depends upon a turpentine-like volatile oil.

Fluidextractum Grindeliæ .....30 to 60 minims (2–4 mils).

Therapeutics.—Grindelia has been largely used, often with alleged excellent results, in asthma, and in bronchitis associated with a tendency to bronchial spasm. It is often probable that in these cases it acts chiefly by stimulating the mucous membrane. It is also

employed in chronic bronchitis, especially of the aged, and is said to do good. It has been employed in whooping-cough. In asthma it is used in conjunction with stramonium leaves, which are mixed with saltpetre so that it will burn, and the fumes inhaled.

Grindelia also enjoys a popular reputation as a local application for dermatitis caused by the *Rhus toxicodendron* and similar plants.

BALSAMS.

Materia Medica.—The balsams of Peru and of Tolu are obtained from two closely related trees, the *Toluifera pereiræ* and the *T. balsamum* respectively, both of which are indigenous to Central America. The balsam of Peru occurs as a viscid brownish fluid with a fragrant, somewhat vanilla-like, odor and a warm bitterish taste; the balsam of Tolu is of a more solid consistency, when fresh being a plastic solid, but becoming hard and brittle after keeping. Its color is a yellowish brown, and the odor and taste similar to that of balsam of Peru, but more pleasant. Each of these balsams contains a peculiar resin, but their therapeutic value depends upon the presence of benzoic and cinnamic acids, as well as benzyl esters of these acids.

Official Preparations:

Balsamum Tolutanum .....15 to 30 grains (1–2 Gm.).
Tinctura Tolutana (20 per cent.).....½ to 1 fluidrachm (2–4 mils).
Syrupus Tolutanus (1 per cent.).....½ to 1 fluidounce (15–30 mils).

Therapeutic Uses.—They are used in chronic and subacute catarrhs of the respiratory and genito-urinary system. For internal use the balsam of Tolu is generally preferred because of its grateful taste, and is very much used as a flavor to cough mixtures in the form of the syrup. The balsam of Peru is also employed to a large extent as a stimulant application to sluggish and unhealthy ulcers.

CUBEB.

Materia Medica.—The unripe fruit of *Piper cubeba,* a climbing plant of Java and other portions of the East Indies. These berries are blackish-veined, about the size of a small pea, and have attached to them a short stalk three or four lines long. Their odor is aromatic and peculiar; their taste warm, camphoraceous, and peculiar. They contain *cubebic acid, cubebin,* volatile oil, and resin, and are fully represented by the official oleoresin. Cubebin seems to be without effect upon the system.

Therapeutics.—Cubeb has been used in the past to a considerable extent as a stimulant in chronic inflammations of the mucous membranes, especially of the bronchi and urethra. It has, however, largely been replaced by other drugs in this condition, and to-day it is scarcely

used except in the form of lozenges as a local remedy in various congestions and inflammations of the mouth and throat.

Oil of Santal (*Oleum santali*) is a pale yellowish, strongly aromatic volatile oil, of a pungent, spicy taste, from the distillation of the wood of *Santalum album*. It is insoluble in water, but readily soluble in alcohol. When pure, it is a local irritant and probably capable of affecting the general system, although its physiological action has not been properly investigated.

The oil of sandalwood, although an efficient stimulant expectorant in chronic bronchitis, is rarely employed to-day for any purpose save as an internal remedy in the treatment of gonorrhœa. It is, perhaps, more widely employed in this condition than any other internal remedy.

The dose is from ten to twenty minims in capsule or in an emulsion, three or four times a day.

COPAIBA.

Materia Medica.—This oleoresin obtained from *Copaiba Langsdorffi* and other species of copaiba, large trees growing in Brazil, is a yellowish liquid, of varying viscidity according to age, having a strong, terebinthinate, peculiar odor, and a bitter, burning, disagreeable taste. It mixes uniformly with absolute alcohol and volatile and fatty oils, and is readily dissolved by ether. It contains a volatile oil, a small quantity of soft, viscid resin, about fifty per cent. of a hard, acid resin, and a peculiar crystallizable acid, *copaivic acid*, which is unimportant, the activity of the drug depending upon the oleoresin.

The dose of copaiba is ten to twenty minims (0.6–1.2 mils), usually administered in capsules.

Physiological Action.—Aside from its local effects, copaiba has little influence upon the system. When taken in large dose it may irritate the stomach sufficiently to produce vomiting and purging, and, being eliminated chiefly through the kidneys, there are evidences of irritation of the urinary tract, as shown in the burning sensation in the urethra and occasionally strangury. It is eliminated slowly, the oil having been found in the urine as much as four days after its ingestion.

In persons who are taking large doses of copaiba the urine gives a precipitate upon the addition of nitric acid which may be confused with albumin. Also, there appears in the urine a substance known as copaiba-red, which is capable of reducing copper, and may therefore lead to error in the diagnosis of diabetes.

Therapeutic Uses.—Copaiba is at present used almost solely in the treatment of the advanced stages of gonorrhœa. It is, however, occasionally used in the treatment of catarrh of other mucous membranes, such as chronic diarrhœa and chronic bronchitis, with other expectorants. Locally it is sometimes employed for the relief of chilblains.

EXPECTORANTS.

Brautigam and Nowack .....C.K.M., 1889, xxiv.
Buffington .....A.J.M.S., Jan. 18, 1886.
Henderson .....J.P., Ex. T.
Kobert .....Chem. Centralblatt, 1893, i, 32.
Murrell .....B.M.J., Dec., 1885.

TREATMENT OF ACUTE BRONCHITIS.

Acute bronchitis may be divided into two stages. In the first there is an active diminution of the bronchial secretions, the mucous membrane being red and dry. On account of the irritation of the sensory nerves, there is considerable cough, which, because of the lack of secretions, is peculiarly unpleasant and at times even painful. As the disease progresses and the acuteness of the irritation passes off, the secretions gradually become re-established and at length are excessive, being ordinarily mucopurulent in character. The indications in the first stage are for the use of sedative remedies to allay the acute irritation, and for drugs which will relieve the distressing cough. Ordinarily, however, the latter remedies are not needed, if proper treatment is adopted for the relief of the irritation of the mucous membrane, and may prove harmful, because most of those remedies which are used for the purpose of checking cough also check the bronchial secretions.

The most soothing application for a mucous membrane is its own healthy secretion, and the physician's efforts in acute bronchitis, therefore, should be directed mainly towards the increase of bronchial secretion. For this purpose the most useful remedies we have are the nauseating expectorants. Among these, antimony is too depressant in its influence on the circulation to be used except in sthenic individuals. Apomorphine is a valuable drug in these conditions, but its instability when in solution interferes greatly in its use. Solutions of apomorphine of more than twenty-four hours should not be employed. The drug which is most frequently serviceable is ipecac, which may be given in the form of the syrup in doses of from fifteen to thirty minims. With it may be combined advantageously potassium citrate, which by virtue of its salt action tends to increase the bronchial secretions and, circulating in the blood partially as a carbonate, tends to preserve the alkalinity of the secretions and therefore their fluidity.

Much benefit may also be derived, especially in those cases where the larynx and trachea are involved, by inhalation of warm aqueous vapors. This may be accomplished in several ways. For instance, the patient may hold his face over a basin of boiling water and inhale the vapors as they arise. More active effects may be obtained by the use of the so-called bottle inhaler, which is made upon the principle of the chemical wash bottle with two tubes, one of which dips down below the surface of the water and the other ends in the air space at the top of the bottle. The patient taking the short tube into his

mouth and inspiring, the air bubbles up through the water and is inspired saturated with aqueous vapor. In using this method care should be observed not to have the water too hot, as it is possible to scald the mucous membrane. The most efficient means, however, of applying aqueous vapor is with the steam atomizer. (See Fig. 6.)

Volatile antiseptics, such as benzoin, menthol, or eucalyptol, may be added to the hot water with any of these apparatuses.

In the second stage the indications are for stimulant antiseptic treatment which shall restore tone to the passively dilated blood-vessels and antagonize the growth of bacteria. Ammonium salts are very frequently prescribed at this stage, but it is doubtful whether they exercise any influence beyond their salt action. Any of the stimulant expectorants, such as terpin hydrate, eucalyptus, or creosote, may be employed.

Treatment of Cough.—When from disease or from other causes obnoxious materials, be they secretions or foreign matters, accumulate

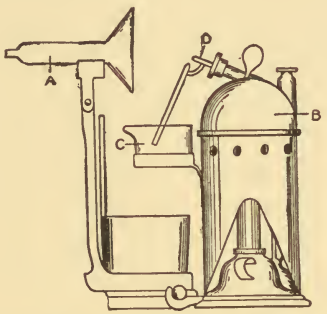


FIG. 6.—Steam Atomizer. When steam is generated in boiler *B*, passing out through tube *D*, it draws up any medicament which may be placed in cup *C*; the mingled warm aqueous vapors and drug are inhaled by the patient through *A*. The mode of treatment is of especial value in acute laryngitis and bronchitis.

in the bronchial tubes, cough is necessary for their expulsion, so that in a large proportion of cases no treatment of cough is desirable. On the other hand, there are cases in which, owing to excessive irritability of the pulmonic mucous membrane, the amount of cough is out of all proportion to the amount of material to be expelled. Under these circumstances the symptom is not only annoying, but also, by irritating the mucous membrane of the lungs and by exhausting the patient, directly harmful. In another set of cases, owing to muscular weakness and to lack of irritability of the mucous membrane, the cough is not sufficient for the expelling of the secretions, which gradually accumulate in the lungs, fill up the bronchial tubes, and finally, it may be, cause death by a process comparable to that of drowning.

It is plain that the medical practitioner must study in each individual case the relations between the cough and the amount of work required; so that if the cough be excessive it may be allayed,

if it be insufficient it may be stimulated. For the purpose of allaying cough, soothing vapors or liquid may be applied to the respiratory mucous membrane by inhalations, but in the majority of cases internal anodynes are necessary.

In some instances the cough is maintained by an excessive irritability in the upper throat and air-passages, so that demulcents such as liquorice are very useful, or relief may be obtained by sipping a mixture composed of glycerine and whiskey, each one part, with two to four parts of water.

The anodyne substances which are employed for the relief of cough are hydrocyanic acid, belladonna, hyoscyamus, chloroform, the bromides, morphine, codeine, and heroine. The action of hydrocyanic acid is too brief for the remedy to be of practical value. Belladonna, unless locally applied by means of atomization, is very uncertain in its action and of entirely secondary importance; superior to it is hyoscyamus, although even full doses of this remedy often are ineffective. Chloroform, in doses of ten to fifteen minims (0.6–0.9 C.c.), sometimes acts most happily, but must be given at very short intervals on account of the fugaciousness of its influence, and is more useful in combination than alone. The bromides in full doses are often effective, and may well be combined with chloroform; in some cases they are too depressant. Much more certain in its influence than any remedy yet mentioned is opium; its tendency to check secretion forbids its use, however, in a very large proportion of cases, notably in those in which there is persistent dryness of the bronchial mucous membrane, whether this dryness represents the first stage of an acute bronchitis or whether the case be one of a continuing subacute bronchial irritation so frequent in neurotic individuals. Moreover, the usefulness of opiates is further limited by their tendency to derange digestion, and in chronic cases by the danger of forming the opium habit. Diacetyl ester of morphine (heroine) is a very powerful sedative to the respiratory center and is probably at least equally valuable with morphine for the relief of cough. In corresponding dose it is less likely to check secretion or to cause constipation, although both effects may be observed from its use. As regards the liability of formation of a habit, there are not sufficient data to allow a positive statement, but I believe it is less likely to give rise to a habit than morphine. Codeine is also frequently of service as a cough sedative, for, while less efficacious than either morphine or heroine, it is comparatively free from the drawbacks of these remedies.

DRUGS WHICH DIMINISH SECRETION.

There are two classes of drugs which are used for the purpose of lessening secretion. The first group, which is typified by atropine, acts when administered internally; the second group, the astringents, must be applied directly to the affected part.

ATROPINE GROUP.

The Solanaceæ, or nightshade family, is remarkable for the range of purpose to which its various plants have been put. It furnishes the hungry with such valuable foodstuffs as the potato and tomato, the care-worn with the popular narcotic tobacco, the Thugs of India with the stupefying poison dhátura, and medicine with many valuable drugs.

The medicinal plants of this family at present official are belladonna, stramonium, and hyoscyamus.

In the past there has been much contradiction concerning the chemistry of these plants, but recent investigations have cleared away much of the confusion upon the subject. While there are a number of alkaloids of secondary importance, those which are of clinical interest belong to one of two pairs of isomeric compounds, which we may denominate as the hyoscyamine and scopolamine groups. The differentiation of the alkaloids in each group has been made possible by the use of the polariscope.

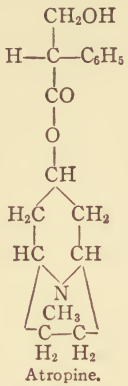
When a ray of light is made to pass through a piece of feldspar, it is broken up, so to speak, into a series of parallel sheets, so that when two prisms of feldspar are set at right angles to each other, no light can be perceived. Certain substances have the power, when in solution, of rotating the sheet of light rays, so that if the light is passed first through the polarizer and then through a column of the solution of an optically active body, the light can be perceived even when the analyzer, as the second prism is called, is set at an angle to the polarizer. A substance which does not affect polarized light is said to be optically inert, one which turns it towards the right, dextro-rotatory, and one which turns it towards the left, lævo-rotatory. The term " racemic " is applied to the optically inert isomer.

The alkaloid atropine is optically inert, but appears to be a mixture of a lævo-rotatory and a dextro-rotatory body. Although the lævo-rotatory hyoscyamine occurs free in many plants, the dextro-rotatory form has never been found naturally, but has been prepared. As it is possible to have mixtures of the dextro- and lævo-rotatory bodies in varying proportions, it is evident that we can have hyoscyamines of all degrees of optical activity. All of these bodies are isomeric; that is, they have the same percentage composition. A similar relation holds in the case of scopolamine, but the Phamacopœia recognizes only the optically active form. The term "atroscine" is sometimes applied to racemic scopolamine, analogous to atropine. I shall use the term " scopolamine " in the official sense for the lævo-rotatory variety and the term " atroscine " for the optically inert form.

The hyoscyamines are tropic acid esters of tropine; the scopolamines are tropic acid esters of scopoline (also called oscine). Scopoline differs from tropine in that two atoms of hydrogen in the latter have been replaced by one of oxygen. The appended graphic formula shows the structure of atropine.

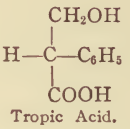
Various artificial esters of tropine have been prepared. These are

called tropeins. One of these tropeins is recognized by the United States Pharmacopœia under the name of homatropine. This is an artificial alkaloid differing from atropine in its chemical structure in the substitution for tropic acid of its homologue mandelic acid.



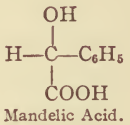
Atropine.

Tropic Acid.



Tropic Acid.

Tropine.



Mandelic Acid.

Atropine and hyoscyamine, or optically active and inert hyoscyamines, are very similar in their effects upon the system, although, as will be pointed out, there is a quantitative difference. While it is a common custom to speak of the active principle of belladonna as being atropine, it is doubtful whether much atropine exists in belladonna as such; recent chemical studies have led to the belief that the dominant alkaloid of belladonna is really hyoscyamine, but that it is converted, during the process of extraction, into the non-polarizing form of atropine. This fact is of more than merely academic importance, as it is the probable explanation of the well-recognized clinical fact that belladonna and atropine are not exactly the same in their medicinal properties.

All of the official plants of this series appear to contain both atropine (hyoscyamine) and scopolamine. Only in hyoscyamus is there sufficient scopolamine to affect the medicinal virtues of the plant, and even in this drug the action is dominated by the hyoscyamine.

Materia Medica.—The official plants belonging to this family are the *Atropa belladonna,* the *Datura stramonium,* and the *Hyoscyamus niger.*

Atropa belladonna (deadly nightshade) is an herbaceous perennial native to Europe. The leaves and root are both official. The leaves (*Belladonnæ folia*) are four to five inches long and two to four inches broad, ovate, with entire margin. The root (*Belladonnæ radix*) occurs in brown wrinkled pieces about the thickness and length of the finger, somewhat tapering. Belladonna leaves should contain not less than 0.3 per cent. of mydriatic alkaloids, of which the most important are atropine and hyoscyamine. The root should contain 0.45 per cent. of the same alkaloids.

Stramonium is the leaves of *Datura stramonium,* or jimson weed, a common plant growing in waste places in many parts of the United States. The plant is characterized by the vivid green color of its leaves, white to purplish flowers, and a peculiar thorny fruit which gives to it the name of "thorn apple." The leaves are from four to five inches long and deeply toothed.

Hyoscyamus is the dried leaves and flowering tops of the *Hyoscyamus niger* (henbane), a plant which is a native of Europe and Asia and has been naturalized, to a certain extent, in this country. It is a biennial herb, growing from two to four feet in height, pubescent stem and leaves, the latter being from two to ten inches long and one to four inches broad, coarsely toothed and lobed. The flowers, which grow on one-sided leafy spikes, are of a yellowish color and beautifully variegated with purple markings, the anthers and style also being purple. The leaves occur in broken pieces of a grayish-green color, of a heavy narcotic odor, and a bitter, nauseous taste. They contain both hyoscyamine and scopolamine. The Pharmacopœia directs that it shall contain not less than 0.065 per cent. of total alkaloids.

Official Preparations:

Extractum Belladonnæ Foliorum.....⅛ to ½ grain (0.008–0.03 Gm.).
Tinctura Belladonnæ Foliorum (10 per cent.).10 to 30 minims (0.6–2.0 mils).
Fluidextractum Belladonnæ Radicis.....1 to 2 minims (0.06–0.12 mil).
Linimentum Belladonnæ (5 per cent. camphor in fluidextract).....External use.
Emplastrum Belladonnæ .....External use.

Extractum Stramonii .....⅛ to ½ grain (0.008–0.03 Gm.).
Tinctura Stramonii (10 per cent.).....10 to 30 minims (0.6–2.0 mils).
Unguentum Stramonii .....External use.

Extractum Hyoscyami .....1 to 3 grains (0.06–0.19 Gm.).
Fluidextractum Hyoscyami .....3 to 5 minims (0.2–0.3 mil).
Tinctura Hyoscyami (10 per cent.).....½ to 2 fluidrachms (2–8 mils).

The following alkaloidal preparations are also recognized:

Atropina .....$^1/_{200}$ to $^1/_{60}$ grain (0.3–1.0 Milligm.).
Atropinæ Sulphas .....$^1/_{200}$ to $^1/_{60}$ grain (0.3–1.0 Milligm.).
Oleatum Atropinæ (2 per cent.).....External use.
Hyoscyaminæ Hydrobromidum .....$^1/_{200}$ to $^1/_{60}$ grain (0.3–1.0 Milligm.).

Physiological Action.—The action of atropine consists in a depressant effect on the endings of the autonomic nerves—those which are stimulated by pilocarpine (see page 46)—and a stimulant effect upon certain nerve-centers. Hyoscyamine appears to differ from atropine in that it acts relatively much more powerfully in its influence upon nerve-ends and more feebly centrally. The results of these actions on the various functions of the body can best be studied separately.

Secretion.—Atropine checks the secretion of the salivary, sweat, lachrymal, gastric, pancreas and suprarenal glands, and probably all true glands of the body, except the mammary and the kidneys, which are not supplied by autonomic nerves. The mode of action upon glands may be exemplified by the salivary.

The administration of atropine in sufficient quantity entirely arrests the secretion of the saliva, and stimulation of the chorda tympani will no longer give rise to a flow of saliva. Not only is the quantity of saliva diminished, but also that of the solids, and there is even a fall in the percentage of solid matter in the saliva. That the gland cells themselves are not affected, however, is shown by the fact that stimulation of the sympathetic nerve will cause a renewed secretion; therefore, we conclude that the drug has acted at the junction point between the chorda tympani and the gland cells.

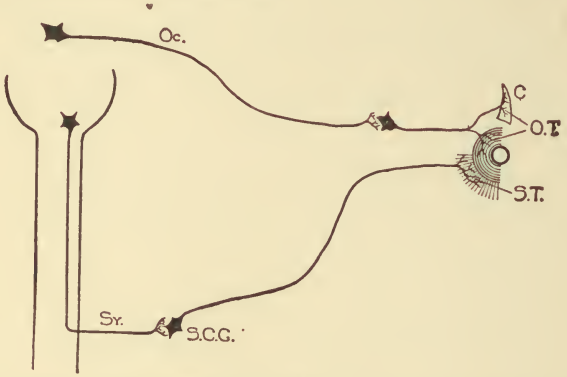


FIG. 7.—Diagram to show the innervation of the eye. Oc, Oculomotor nerve running to the constructing fibers of the iris and to the ciliary muscle. Sy, Sympathetic nerve running to the radial fibers of the iris. C, Ciliary muscle. O.T., Peripheral endings of the oculomotor nerve. S. T., Peripheral endings of the sympathetic nerve. S. C. G., Superior cervical ganglion. Atropine and scopolamine paralyze O. T., cocaine stimulates S.T., pilocarpine and physostigmine stimulate O.T.

Eye.—If atropine is instilled into one eye it will give a dilatation of the pupil on that side with a paralysis of accommodation. That the action is upon some structure within the eyeball itself is shown by the following facts: When instilled into one eye it causes dilatation of the pupil only on the side to which it is instilled; it is capable of dilating the pupil after section of both the trigeminus within the skull and the sympathetic within the neck; and in the frog atropine will produce dilatation of the pupil after removal of the eye from the body.

After dilatation of the pupil by atropine electric stimulation of the oculomotor nerve will no longer give rise to a narrowing of the pupil, although if the electrodes are applied directly to the muscle of the iris it can be caused to contract. It is evident, therefore, that atropine has paralyzed the peripheral endings of the oculomotor nerve.

Whether or not there is also a stimulant effect upon the sympa-

thetic nerves has been the subject of much dispute, but the present evidence tends to show that these are not affected. In the first place, either electrical stimulation of the sympathetic nerve or the instillation of cocaine will lead to a further widening of the full atropinized eye. In the second place, Schultz has shown that after extirpating the superior cervical ganglion on one side and waiting a sufficient time for degeneration of the peripheral endings of the sympathetic nerve, atropine dilates the pupils equally on both sides; if the drug had acted upon the pupil-dilating mechanism, we should have expected a greater degree of widening in the unoperated eye. Against these experimental facts the only argument of any weight is the experience of clinicians concerning the force of dilatation of the pupil under atropine which is sufficient to break up adhesions within the eye. This, however, can scarcely be classed as scientific evidence.

Because it dilates the pupil atropine tends to increase intra-ocular pressure. The ciliary muscle being supplied by the oculomotor nerve, accommodation is also destroyed by atropine.

Circulation.—The characteristic effects of atropine upon the circulation in man are a great increase in the rate of the pulse and an elevation of the blood-pressure.

The increase in the pulse-rate does not occur after section of the pneumogastric nerve, and it is absent in those animals, such as the rabbit, whose inhibitory mechanism is not tonically active. It is evident, therefore, that the increased pulse-rate is due to paralysis of some portion of the inhibitory apparatus, and since the atropinized heart cannot be slowed, either by electrical stimulation of the pneumogastric nerve or by the administration of drugs, such as muscarine, which excite intracardiac inhibitory fibers, it is evident that the atropine must act upon the extreme endings of the vagus.

After small doses the rise in pressure seems to be the result chiefly of the increased rapidity of the heart-beat, but larger quantities of atropine will cause an elevation in the blood-pressure even after previous section of the pneumogastric nerve, although, as we have seen, the pulse-rate is not increased. The rise in pressure is, however, entirely prevented or rendered insignificant by previous section of the spinal cord, and must, therefore, be due to a stimulant upon the vasomotor centers in the medulla. The vascular constriction which follows atropine is limited chiefly to the splanchnic area; indeed, there is often in the skin a widening of the blood-vessels, which is shown by the violent flushing which follows full doses of the drug.

As to whether or not atropine stimulates the heart muscle there has been much difference of opinion and the evidence is not sufficient to allow of positive conclusions, but the probability is that there is a slight effect on the heart muscle.

After large doses the blood-pressure falls from a depressant effect probably on both the vasomotor system and the heart.

Nervous System.—Atropine excites a number of nerve-centers in

the brain, the medulla, and the spinal cord. The character of this stimulant in these various areas differs from that of most other drugs which affect the same centers. Thus in the case of the brain, while it is the intellectual centers which are excited, they are not exalted to any better functional activity as they are by caffeine, but the thoughts become rambling, incoherent; atropine produces an active delirium, and in no dose is there any evidence of an increased intellectual power.

The stimulant effect upon the medulla is seen especially in its influence on the vasomotor and the respiratory center. There is also some reason to believe that it excites the cardio-inhibitory center, although stimulation of this center will be generally hidden by the peripheral paralysis of the pneumogastric nerve. In the normal animal the increase in respiration under the influence of atropine is sometimes very marked, but in presence of depressant poisons the drug is comparatively feeble.

In the frog atropine is capable of exciting the spinal cord sufficiently to lead to convulsions, but, although in cases of atropine poisoning increased reflexes have been noted, spinal convulsions are not caused in man by the drug. In the frog atropine acts as a depressant to the peripheral endings of the motor nerves, although it rarely leads to such complete paralysis as is seen after curara. This effect has not been observed in man from the internal administration of the drug, but may be caused by its local application directly to the nerve. The drug appears also to have some power over the sensory nerve-endings.

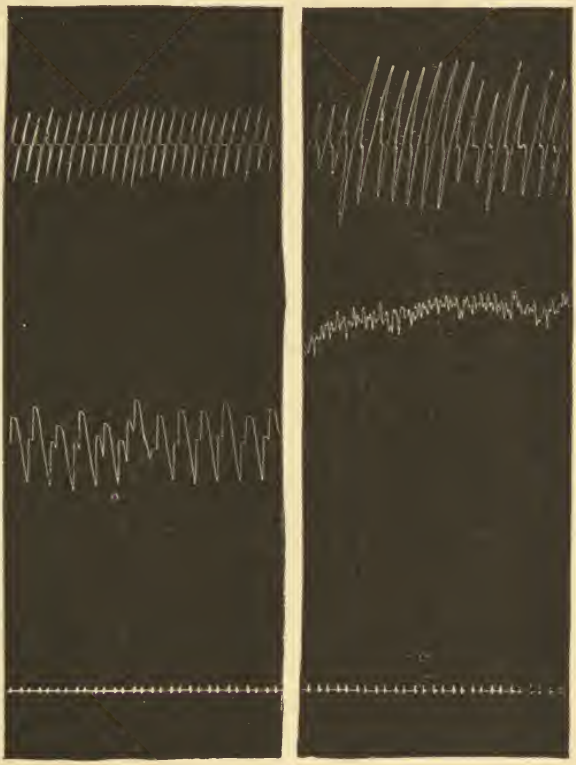
Involuntary Muscle.—While atropine exercises a marked influence on the movements of the unstriped muscular tissue, the precise seat of its action is not clearly understood. The subject has been extensively investigated in the intestinal tract. Various authorities have attributed the effects of atropine to actions upon the intestinal branch of the vagus, which is generally believed to be a motor nerve for the intestinal muscles, or on the splanchnic nerves, which are believed to furnish inhibitory impulses to the bowels, but all the observed facts are explicable on the ground of an effect upon structures within the intestine wall itself. According to Magnus, the moderate dose of atropine stimulates the plexus of Auerbach, which lies between the longitudinal and circular layers of the intestine, giving rise to an increased vigor of the peristaltic movements, but especially rendering them more regular. After larger quantities it secondarily paralyzes this same nervous mechanism, checking the peristaltic movements, although the latter may be excited by those agents which stimulate directly the muscle. After the local application of large quantities there is eventually a paralysis, even of the muscle substance, but to produce this effect requires doses much larger than could be administered internally.

The motor supply for the bronchial muscles is through the pneu-

mogastric, and as atropine paralyzes the pulmonary as well as the cardiac branch of this nerve it produces a relaxation of the bronchi.

Therapeutic Uses.—Atropine and hyoscyamine are used in medicine for four purposes: to check secretion; to relax spasm; to stimulate the circulation, and to stimulate respiration.

Secretion.—Probably the first evidence of the general action of these alkaloids is their effects upon glandular activity. In the night-



(Normal.) (After atropine.)

FIG. 8.—Effect of atropine on the pulse and respiration. Atropine increases the rate of the pulse by paralyzing inhibition; it stimulates the vasomotor centers, causing a rise of the blood-pressure. It also increases the respiration. Time marker indicates 1 second.

sweats of phthisis and similar adynamic conditions they are the most potent and certain remedies that we possess. In acute coryza, and often also in hay fever, atropine, if pushed to the physiological limit, will give much relief by checking excessive secretion, and appears also at times to lessen the congestion of the mucous membrane. In overaction of the salivary glands, as seen in mercurialism, atropine and its congeners are frequently of great service. In hyperchlorhydria

they are the only remedies which seem to exercise any curative influence. On the mammary gland the action of atropine is much less marked; indeed, some authorities deny that it affects the secretion of milk at all, but it is nevertheless widely employed wherever it is desirable to check the secretion of milk, as in acute inflammatory conditions of the breast. Upon the kidneys atropine has no direct influence.

Spasm.—In local spasm of the voluntary muscles, as torticollis, atropine has been injected deeply into the muscle with, in some cases, apparent benefit. Whatever action it exercises in these conditions must be due to its depressant action upon the peripheral motor nerves. In general convulsions it is of no value whatsoever.

In spasms of the unstriped muscle atropine and its congeners are among the most serviceable remedies which we possess. It is largely used in conjunction with cathartics, its regulating action tending not only to prevent the griping, but also to enhance the laxative effect; similarly, in lead colic, by relaxing the spasm of the intestines it will often relieve the constipation. In the colic due to the passage of a stone either through the gall-duct or ureter the administration of atropine in full dose not only aids in the passage of the stone, but also lessens the pain; in these conditions it should be combined with morphine.

Although not truly a curative in asthma, as a palliative during the paroxysm atropine is among the most valuable remedies that we possess. While it is possible by the internal use of the drug to obtain the paralytic effect upon the pulmonary branches of the vagus, such large doses have to be given as to cause serious disturbance of other functions of the body, and it is therefore highly desirable to apply the drug locally. This can best be accomplished through volatilization by means of heat. For this purpose one of the cheaper sources of atropine, as for example the stramonium leaf, may be mixed with saltpeter and burned either in a saucer or in a pipe, the patient inhaling the fumes as deeply as possible. Nearly all of the proprietary asthmatic powders upon the market contain stramonium or some allied plant.

The nocturnal enuresis of children is frequently due to an excessive irritability of the bladder, in which case atropine given in full dose is often of great service, being brought, through its excretion in the urine, into direct contact with the walls of the bladder. It has also been used with more or less success in other forms of spasm, as in laryngismus stridulus, whooping-cough, and spasmodic dysmenorrhœa.

Respiration.—As a respiratory stimulant atropine is a useful, but somewhat overestimated, remedy. It has been chiefly employed in the treatment of narcotic poisonings, especially opium or morphine poisoning. While by no means a specific in this condition, as was at one time largely believed, if properly employed it is of service. It should be remembered, however, that while the moderate dose of atropine is a stimulant to the respiration the large dose is depressant, and if 1/50 of a grain does not produce the desired increase in the

breathing it is not advisable to give more, because by so doing one may add to the embarrassment of the respiratory center. In a general way atropine is a less certain stimulant to respiration than either strychnine or cocaine, but is frequently of adjuvant value.

Circulation.—In cases of acute circulatory failure dependent primarily upon vasomotor weakness, such as surgical shock, atropine may prove useful because of its stimulating effect upon the medulla. It is necessary in these conditions, however, to give larger doses than are required to check secretion, and, therefore, if sufficient of the drug is used to stimulate the circulation, much discomfort may be produced through the drying of the mucous membrane of the mouth and throat.

In cases of bradycardia, due to poisoning by inhibitory stimulants, as veratrum or muscarine, atropine is of great service; indeed, in cases of poisoning by those mushrooms whose toxicity depends upon muscarine it may be regarded as a life-saving remedy. In poisoning by the digitalis group, however, while in the stage of slow pulse atropine will increase the pulse-rate, its use is not to be advised, as it probably increases the danger of cardiac arrest by these drugs. On the other hand, where the slow heart action is due to diseases of the muscle itself, atropine is of no service; indeed, its use has been suggested as a means of diagnosing between myogenic and neurogenic bradycardia.

Eye.—Atropine is used by ophthalmologists, first, to dilate the pupil for the purpose of ophthalmoscopy; second, to paralyze accommodation for the purpose of correcting errors in refraction; third, to rest the iris and prevent the development of synechia in iritis and iridocyclitis; and, fourth, to rest the eye in various forms of keratitis and corneal ulcers. Because of the slowness and persistence of its effects, for the first two mentioned uses it has been largely replaced by the more rapidly acting mydriatics, but in cases of diseases of the eye this very slowness of action gives it the preference. After the installation of a one per cent. solution of atropine sulphate in the eye the pupil begins to dilate in about fifteen minutes, and reaches its maximum in about twenty-five minutes. The accommodation begins to disappear in about half an hour, and is usually completely lost in an hour and a half to two hours; the effects of a single application may last for from three days to a week before they completely disappear.

Externally.—Atropine is widely used, especially in the form of the belladonna plaster, as a local anodyne in various neuralgic and rheumatic pains. What slight benefit its local application can confer depends upon its paralytic effects on the sensory nerve-endings, which is, after all, but a comparatively feeble one. It must be remembered that it is capable of being absorbed when applied either in the form of a plaster or an ointment, and several cases of poisoning have followed its external application.

Administration.—As mentioned above, hyoscyamine is proportionately more powerful in those effects which depend upon paralysis of the peripheral endings of the autonomic nerves than is atropine, so that theoretically it should be the remedy of preference for the purpose of checking secretion and relaxing spasm. Practically, however, by giving somewhat larger doses of atropine we can produce effects upon these nerve terminals with little or no perceptible evidence of the action upon nerve-centers, and, although perhaps theoretically preferable, hyoscyamine is used clinically to only a slight extent. Whenever the drug is employed to reach an organ through the circulation the alkaloid itself should be given the preference, and in cases where promptness of action is desirable should be given hypodermically. On the other hand, where the drug is being used for its effects upon the alimentary tract, especially upon the stomach, the galenic preparations are usually preferred, on the theory that, being less slowly absorbed, some direct local action may be obtained.

Toxicology.—An extraordinary number of people show marked idiosyncrasy towards the alkaloids of the solanaceous group, and a mild degree of poisoning is not uncommon from therapeutic doses of the drug. It is to be remembered, also, that several of our native plants, notably the jimson weed, contain principles allied to atropine, and accidental cases of poisoning are not uncommon. Happily, poisoning by these substances, although the symptoms are often very alarming, rarely end fatally.

The earliest symptoms of atropine poisoning are a dryness of the throat and mouth, with redness of the fauces, dilated pupil, disordered vision, and possibly diplopia. The pulse is excessively rapid and hard; the skin is warm and dry, and frequently an erythematous rash appears on the face and neck and sometimes spreading over the body. This eruption resembles that of scarlet fever, but lacks the punctation and is usually not followed by desquamation. Early in the poisoning there may be forcible expulsion of urine, but later there is commonly retention. The most striking symptom in a well-developed case is the peculiar, talkative, wakeful delirium, sometimes associated with hallucinations or illusions. Sometimes the delirium is wild and the patient almost uncontrollably violent. Respirations are at first increased in both rate and depth, but after very large doses may become slow and shallow, death, if it occurs, being immediately due to asphyxia. In cases of fatal poisoning, stupor and muscular paralysis finally develop, sometimes preceded by convulsions.

The diagnosis, if in doubt, may be confirmed by instilling a few drops of the urine into the eye of a cat or other animal, when if the case is atropine poisoning the pupil will be dilated. While this physiological test furnishes sufficient evidence for a working diagnosis, it merely proves that the poisoning is by some mydriatic substance, not necessarily atropine. Morel calls attention to a sort of laryngitis

produced by poisonous doses of belladonna, characterized by pain in the larynx, roughness of voice, and the expectoration of minute, pearly, tough pellets. Raphael has noted glycosuria as a symptom of belladonna poisoning and has experimentally produced the condition with atropine in rabbits.

In the treatment of belladonna or allied poisoning the stomach should be emptied at once, either by a rapidly-acting emetic, as zinc sulphate, or by the use of the stomach-pump. The best chemical antidote is the compound solution of iodine, which may be given in doses of 6 minims; in the absence of this, tannic acid, although much less efficient, may be administered in 20-grain doses. For the delirium morphine may be used cautiously, although it must be remembered that the real danger in atropine poisoning is from depression of respiration. Pilocarpine is the physiological antagonist to atropine, and, while I know of no cases in which it has been actually employed, it would probably be of service. As stated above, the only real danger in atropine poisoning is failure of respiration, and if there is evidence of this strychnine and caffeine may either or both be employed with beneficial effect, and if these fail artificial respiration should be practised and persisted in as long as the danger exists.

SCOPOLAMINE.

Found in many of the solanaceous plants, secondary to atropine or hyoscyamine, there is a second alkaloid which differs in its composition from atropine in that two atoms of hydrogen are replaced by one of oxygen. Just as atropine may be regarded as a molecular union of tropine and tropic acid, scopolamine may be considered a molecular union between scopoline, which is an oxytropine, and tropic acid. As in the case of atropine, we have two varieties of alkaloid, one which is capable of rotating polarized light and another which is optically inert, and we may have all grades of rotatory power, precisely as in the case of the hyoscyamines.

The term "hyoscine" was applied by Landenburg to an alkaloid which he discovered in hyoscyamus and which he believed to be a new principle. Subsequently, however, this was shown by Schmidt and by Hesse to be identical with the alkaloid scopolamine previously found in *Scopola atropoides*. Unfortunately the word "hyoscine" has persisted in this country almost to the exclusion of the more correct "scopolamine," and even received official sanction until the Ninth Revision of the Pharmacopœia.

Official Preparations:

Scopolaminæ Hydrobromidum .....$^1/_{200}$ to $^1/_{80}$ grain (0.3–0.8 Milligm.).

Physiological Action.—The effects of scopolamine upon the endings of the autonomic nerves are similar in kind to those of hyoscyamine, although less powerful, but, as in the case of atropine, the

racemic alkaloid is weaker than the optically active; indeed, in ordinary doses, the action on nerve-endings is sometimes almost imperceptible after the exhibition of atroscine.

While these alkaloids resemble atropine in their effects upon nerve-endings, they differ markedly in that they are depressant rather than stimulant to nerve-centers.

Nervous System.—In the higher mammals scopolamine leads generally to the production of sleep, although in the lower mammals, as the rabbit, its hypnotic influence is not manifest. It differs from the ordinary hypnotics in that its action appears to be mainly upon the psychomotor area, and as a true somnifacient it is comparatively uncertain.

In the frog scopolamine produces a lessening of reflex action, which is probably due to a depression of the motor tract in the spinal cord, although certain authorities believe that it is a result of a depressant effect upon the motor nerve-endings.

Circulation.—There has been much contradiction of statement concerning the effects of scopolamine on the circulation, which has only been reconciled through the differentiation between atroscine and scopolamine. Scopolamine, by its depressant influence upon the peripheral endings of the pneumogastric nerve, causes an increase in the rate of the pulse; on the other hand, the optically inert atroscine has little or no effect in ordinary dose, either upon the blood-pressure or pulse-rate, although very large doses may slightly lower the pressure. Neither has any stimulant influence on vaso-motion.

Respiration.—Scopolamine differs markedly from atropine in that in no dose is it stimulating to the respiratory center. While in small doses its effects are comparatively slight, in sufficient quantities it is capable of acting as a respiratory depressant.

Secretion.—Scopolamine, like hyoscyamine, lessens secretion by paralytic action upon the peripheral ends of the glandular nerves, although its effects are much less marked. Although atroscine possesses some influence upon the secretion, as is shown by the dryness of the mouth which it produces at times, its powers are so feeble that in several cases of poisoning the skin has been noted to have been moist.

Eye.—The effects of scopolamine upon the pupil and accommodation are precisely analogous to those of atropine, except that it acts more quickly and less persistently.

Therapeutic Uses.—Scopolamine is used in medicine chiefly as a cerebral sedative and mydriatic. It appears to affect all of the cerebral functions, including intellection, pain perception, and motion. Although when given by itself it is a remedy of only secondary power, it greatly enhances the action of other narcotic substances. Thus Hauchold finds that, although without analgesic powers of its own, it increases the effects of both morphine and urethane. As a somnifacient it is often of service in the milder types of sleeplessness, but is especially valued

in those cases of insomnia in which there is a continual flow of thoughts through an excited brain, and especially when combined with motor excitement, such a condition as is seen typically in acute mania. It has by some even been supposed to exercise a curative tendency in the latter case. When the sleeplessness is due to pain, by itself it is of little service, but smaller doses of morphine are required to produce the desired effect if exhibited with scopolamine. In some individuals the delirifacient action is so marked that the drug may even increase the wakefulness.

As a general nerve sedative it is valuable to quiet the restlessness of neurasthenia and allied conditions and will often assuage the neurasthenic pains. It is also of much value to alleviate the discomfort following the withdrawal of morphine or alcohol in habitual users of these drugs. Scopolamine has achieved a high reputation in the treatment of paralysis agitans, although, in view of our ignorance of the pathogenesis of this disorder, we can formulate no theory as to how it acts.

By its effect upon the motor area of the brain scopolamine is often a useful adjunct in the treatment of epilepsy. While it can by no means replace the bromides, it very frequently will enable the dose of the latter to be reduced. Probably through its influence upon the spinal centers hyoscine is useful in all cases of sexual excitement, such as nymphomania, spermatorrhœa, and allied affections. It is the most certain remedy that we have in ordinary cases of over-frequent seminal emissions, which can usually be controlled by the administration of the one-hundred-and-twentieth to one-eightieth of a grain on going to bed.

In spasmodic conditions of the unstriped muscles scopolamine is usually much inferior to hyoscyamine or atropine, but when there is much pain, as in biliary colic or cystitis, it may often be of peculiar value because of the combination of cerebral and peripheral actions.

As a mydriatic scopolamine is much more prompt and more fugacious than atropine. It is generally employed for this purpose in the strength of 2 grains to the ounce.

In 1900 Schneiderlin suggested the hypodermic injections of large doses of morphine and scopolamine for the production of surgical anæsthesia. In this method doses ranging from one-sixth to one-half grain of morphine in conjunction with from one-hundredth to one-fiftieth grain of hyoscine are injected an hour before the operation. The idea was founded on an erroneous conception of the physiological action of scopolamine, which Smith has shown is synergistic with morphine in its toxic effects. I have collated the reports of nearly 2000 cases, with 9 deaths, giving the frightful mortality of 1 : 221. It is possible that in certain classes of cases the method may occasionally prove of value, but as a routine measure it cannot be too strongly condemned.

In acute diseases of the throat the remedy is contra-indicated.

Toxicology.—The symptoms of scopolamine poisoning are dryness of the mouth, drowsiness, often associated with semi-delirious mutterings and a feeling of giddiness like that of intoxication, the respira-

tions are generally lessened in frequency, the pupils more or less dilated, and the voice hoarse or even partially suppressed. In some instances the pulse-rate is not altered, although in other cases it may be increased in frequency, the difference depending whether scopolamine or atroscine has been ingested. There is usually pronounced muscular relaxation with diminution in reflex activity and loss of coordination. The skin is usually not dry, and the scarlatina-form eruption which is characteristic of atropine poisoning is rarely seen after hyoscine. Death from hyoscine poisoning, uncomplicated by other drugs, is almost unheard of. The treatment is similar to that which has been described under atropine.

HOMATROPINE.

Homatropine is an artificial alkaloid obtained by the condensation of tropine and mandelic acid. The hydrobromide, which is the only official salt, occurs as colorless crystals freely soluble in water and somewhat less so in alcohol.

Homatropine closely resembles atropine in the type of its action. Because of its feeble influence upon the other structures paralysis of the oculomotor nerve can be produced with less liability of constitutional effects with homatropine than with any other drug of this class. Its action is much more transient than that of atropine.

Although it has been asserted that homatropine does not paralyze the vagus, the experiments of Zulick demonstrate that if given in sufficient quantities it does exercise a typical atropine action. It does not, however, appear to exert a stimulant influence upon the medullary centers, and in quantities likely to be employed practically it has no demonstrable influence upon either the circulation or respiration.

Homatropine is used in medicine solely for the purpose of paralyzing accommodation in the correction of errors of refraction. For this purpose one drop of a two to three per cent. solution may be instilled into the eye every fifteen minutes for five or six times; the paralysis of accommodation is ordinarily complete about forty minutes after the last instillation.

AGARICIN.

The white agaric (*Polyporus officinalis*) is a fungus which is found especially on the European larch. Its active principle, agaric acid, when pure, occurs as a yellowish, colorless, and tasteless crystalline powder, sparingly soluble in water. Under the name of "agaricin" preparations of agaric acid containing greater or lesser quantities of impurities have been used in medicine. The dose of pure agaric acid is from ⅙ to ½ grain (0.01 to 0.03 Gm.). Agaricin may be given in doses ranging from ¼ to 1 grain, according to its purity.

In moderate doses agaric acid appears to have little effect on the system, except to paralyze the peripheral ends of the nerves supplying the sweat-glands. It differs strikingly from atropine in that it does not affect the other autonomous nerves.

Locally agaric acid, as well as its salts, is intensely irritant, and when taken into the alimentary tract in large quantities provokes vomiting and purging. When injected into the circulation in toxic doses, it paralyzes the central nervous system, causing motor weakness. There is a primary rise in blood-pressure, probably due to stimulation of the vasomotor center, followed with a secondary fall of pressure.

Agaric acid is used in medicine solely for the purpose of controlling excessive sweating. In the night-sweats of phthisis it is generally regarded as the most efficient remedy we possess aside from the atropine group.

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ASTRINGENTS.

Astringents are drugs which have the power of contracting tissue. Their action is probably due to a superficial coagulation of the albuminous matters of the surface with which they are brought in contact. The coagulum which is rapidly formed, being hard and insoluble, forms a protective covering to the deeper structures, so that the astringent is unable to penetrate more deeply into the tissues and there is little or no damage to the underlying structures. Those precipitants of albumin which form relatively soft or water-soluble combinations act as caustics rather than astringents, because their action is not limited and they go on to the destruction of the deeper layers. Even among those substances which are classed as astringents there are several which if used in a concentrated solution penetrate too deeply and exercise a caustic influence, and very few of them, if used improperly, but are capable of acting as irritants. Their effects upon the circulation in the area with which they come in contact are two-fold: the contraction of the coagulum formed diminishes

the calibre of the blood-vessels, and the walls of the vessels become thickened and less easily penetrated by the cellular elements of the blood, so that the diapedesis of the leucocytes is diminished. Partly as a result of the diminished circulation, but also largely from a direct effect upon the superficial glands, there is a diminution of secretion.

The action of the astringents is always a local one—indeed, a moment's thought will show that it cannot be otherwise, because, being precipitators of albuminous substances, they cannot exist in the blood—and the effort which is sometimes made to affect distant organs by the internal use of astringent remedies is manifestly an attempt at the impossible. Neither our knowledge of the mode of their action nor the effects from clinical use lend the slightest support to any idea of an effect remote from the point of application. A chief indication for the use of an astringent is the existence of relaxation. Frequently, as a result of acute congestions either brought about through the presence of an irritant or from over-function, there is left behind a condition of passive dilatation of the blood-vessels, with excessive secretion and relaxation of the superficial muscular tissues. This condition is seen typically in the throat, sometimes as a result of over-use or improper use of the voice, sometimes brought about by acute infections, and it is in this group of conditions that the astringents find their most characteristic effects.

In acute inflammations astringents are often employed to the detriment of the patient. It must be remembered that inflammation is always due to the presence of an irritant, and until that irritant is removed the condition cannot be considered to be cured. In the majority of cases this irritant is of bacterial origin. Nature's method of destroying these irritant bacteria is by bringing more blood to the part, carrying with it a large amount of those anti-bacterial elements which are found in the blood-serum, and also an abundant supply of the leucocytes, and slowing the blood stream to encourage the escape of the leucocytes and serum from the vessels into the surrounding parts where they may carry on their reparative activities. It is evident that the use of astringents, by diminishing the calibre of the vessels, will lessen the amount of blood flowing to the part, and by their action upon the vessel walls prevent the outwandering of the phagocytic corpuscles. Moreover, as already remarked, many of them are of themselves more or less irritant and may add directly to the inflammation. Some of them, however, are possessed of considerable germicidal properties and may, therefore, become of great service in the treatment of active inflammations, but rather because of their anti-bacterial, than their astringent, effects. Under certain conditions, however, the protective coating of coagulated albumin which is formed by astringents may act as a shield for the underlying tissues against the irritating agent.

Another important use for astringents is to check excessive secre-

tions. These discharges are often due to a passive dilatation of the blood-vessels, occurring either as sequelæ of an acute inflammation or as the result of some disturbance in the vasomotor nervous system. The most common type of such a state is that form of diarrhœa, commonly known as the diarrhœa of relaxation, characterized by copious fluid passages without pain. In this form of diarrhœa the astringents, especially those of vegetable origin, are often of much service. On the other hand, when there is an active inflammatory process going on in the intestines the astringents may often prove harmful rather than beneficial; in the first place, they prevent the secretion of the mucous glands which furnish nature's demulcent, and, secondly, the increased secretion which accompanies the enteritis tends mechanically to wash away the irritant substances which are the cause of the inflammation. However, when the inflammation is very severe, as in Asiatic cholera or sometimes in cholera nostras, the excessive irritation of the mucous membrane may lead to a paralysis of the blood-vessels, the stools becoming serous in character; under such circumstances, although the inflammation is an acute one, at least chronologically speaking, the astringents are urgently indicated.

The astringents are also often of service in local hemorrhage. This they control partly by contracting the blood-vessels, but chiefly through precipitation of the blood proteins, forming a hard coagulum which acts as a plug to the bleeding vessel.

The astringents are divided into two groups, those of vegetable and those of mineral origin. The vegetable astringents owe their virtues to the presence of some form of tannic acid.*

TANNIC ACID.

Under the name of tannins or tannic acids are included a number of vegetable principles, probably glucosidal, which have in common the power of coagulating albumins and of precipitating the salts of iron. Nearly all of the official vegetable drugs contain larger or smaller quantities of some variety of tannin.

The tannic acids may be conveniently divided into two great groups, typified respectively by gallotannic and kinotannic acid, which are distinguishable by the character of the precipitate which they give with ferric salts, the former producing a bluish-black precipitate and the second group a greenish-black or olive-brown precipitate. The substance recognized as tannic acid by the United States Pharmacopœia is the gallotannic acid, and may be regarded as a digallic acid, since when heated in the presence of water it breaks up into two molecules of gallic acid.

Gallic acid belongs to the phenol series, being trioxybenzoic acid.

* It has been suggested that the term tannin be applied to the natural tannin, which is a glucoside splitting up under the influence of dilute mineral acids or certain ferments into glucose and gallic acid, and that the term tannic acid be limited to the digallic acid.

It resembles tannic acid in that it produces a bluish precipitate with iron salts, but differs in that it does not coagulate either gelatine or albumin. It does not, therefore, possess any astringent properties. It occurs as a white or pale fawn colored silky needles, sparingly soluble in water and freely soluble in alcohol.

The official tannic acid—gallotannic acid—is obtained by treating powdered nutgalls with washed ether.

Commercial tannic acid is a light, feathery, non-crystalline powder, usually of a yellowish-white color, a faint odor, and an astringent, somewhat bitter taste, but when absolutely pure it is colorless and free from odor or taste other than that of astringency. Its reaction is acid, and it unites freely with both organic and inorganic bases. It is very freely soluble in water, glycerine, and alcohol. With salts of the alkaloids it produces a whitish precipitate (tannates), soluble in dilute acids; with per-salts of iron, a black (bluish or greenish) precipitate.

Official Preparations:

Acidum Gallicum	15 to 30 grains (1–2 Gm.).
Acidum Tannicum	10 to 20 grains (0.6–1.2 Gm.).
Trochisci Acidi Tannici	Each 1 grain (0.06 Gm.).
Glyceritum Acidi Tannici (20 per cent.)	Local use.
Unguentum Acidi Tannici (20 per cent.)	Local use.

Although tannic acid, like other true astringents, is incapable of absorption, when taken into the digestive tract some of it is changed into gallic acid and absorbed as such; it is probable, also, that some of it may be taken up as a soluble alkaline tannate.

Because of its absorbability gallic acid is often prescribed as an internal astringent in conditions of the kidney, as hæmaturia. It is even claimed that it will diminish the quantity of albumin in the urine in Bright's disease. Its value is, however, doubtful.

Incompatibilities.—Tannic acid has a wide range of incompatibilities. It forms precipitates with the salts of lead, silver, mercury, iron, and antimony. In neutral aqueous solution, it precipitates all of the alkaloids. It combines with the alkaline salts, as sodium carbonate, to form tannates which possess no astringent virtues.

Therapeutics.—Because of the fact that even in concentrated solutions it is incapable of acting as a caustic, and because of its lack of toxicity and because of its power, tannic acid is one of the most widely used of all the astringents, either in the form of the tannic acid itself or of one of the various vegetables containing it. Locally applied it may be used to overcome relaxation, as in spongy gums, mercurial sore mouth, hemorrhoids, and chronic sore throat. To check hemorrhage it may be used whenever the source of the flow can be reached directly, as in epistaxis, hæmatemesis, hemorrhage from the bowels, etc. To arrest excessive secretion it may be employed locally in leucorrhœa, diarrhœa, old abscesses, chronic ulcers, ex-

cessive perspiration, osmidrosis, and various diseases of the skin. It is also often very useful for the purpose of hardening parts exposed to friction, as in cases of sore nipples and tender feet.

When the bowel is to be influenced, preference is usually given over pure tannic acid to one of the crude vegetable drugs, on the ground that the colloid material which is in them will partially protect the tannic acid against the albumins of the stomach, so that it may reach the intestines in an active state.

Tannic acid is useful as an antidote against a number of poisons, including most of the irritant metallic salts, especially those of antimony and iron. It has also been widely recommended as an antidote against alkaloidal drugs. It must be remembered, however, that it will not precipitate the alkaloids from acid solutions and also that the compounds it forms, while relatively insoluble and therefore poorly absorbed, are not completely so, and it is at best only an imperfect antidote.

The following drugs which are recognized by the United States Pharmacopœia depend for their activity chiefly upon some form of tannic acid:

GALLS.

Galls, or, as they are more commonly known, nut-galls, are excrescences which are formed on various species of oak trees following the puncture of certain flies. The form recognized by the Pharmacopœia is that which is found on the *Quercus infectoria,* or dyer's oak, a small shrub native to Asia Minor, which is caused by the puncture of the *Cynips tinctoria.* The insect pierces the young boughs in which it deposits its egg, which irritates the tree to the formation of the tumor which is the gall. The larva which comes from the egg feeds on the vegetable matter on the interior of the gall and eventually passes through the chrysalis stage and becomes a four-winged fly and eats its way out. If the galls are collected before the hatching of the egg, they are of a dark grayish-green color and are known as green or black galls. If collected after the young fly has escaped, they are of a much paler color and are known as white galls. The latter contain a much smaller percentage of tannic acid, and only the dark-colored galls are recognized by the U. S. Pharmacopœia. These are of a dark greenish or grayish color, varying in size from that of a pea to that of a hickory-nut, somewhat globular in shape and commonly marked with tubercles, and sink in water. Galls contain, on an average, from 65 to 70 per cent. of gallotannic acid.

Unguentum Gallæ (20 per cent.).....External use.

The preparations of galls are rarely used internally, but the ointment is a popular local application, especially for the relief of hemorrhoids. The most important use, however, of galls is as the source of the official tannic acid.

GAMBIR.

Under the name of gambir the U. S. Pharmacopœia recognizes the extract which is obtained from the leaves and twigs of the *Ourouparia gambir.* This is a climbing shrub which is found in the eastern part of Asia and the neighboring islands. The extract is prepared by the natives from the leaves and twigs of the plant with boiling water. It occurs in the form of reddish-brown cakes or irregular, brittle masses; its taste is very astringent, at first bitter and after sweetish. It is odorless, soluble in water, and about 60 per cent. of it in alcohol. It contains approximately from 30 to 50 per cent. of catechu-tannic acid. The only official preparation of gambir is the compound tincture, which contains 5 per cent. of gambir and 2½ per cent. of cinnamon.

Tinctura Gambir Composita (5 per cent.).....2 fluidrachms (8 mils).

For the reasons pointed out above, the tannin of gambir and other vegetable astringents is less readily rendered inert by the gastric and intestinal contents and therefore is more efficient where an action upon the bowels is desired. The compound tincture affords an agreeable and active astringent for use in various forms of diarrhœa in which tannin is indicated. The cinnamon not only improves its flavor, but also adds to the astringency.

KINO.

Kino appears in the form of irregular, small, brittle pieces of a ruby-red or brownish-red color with a sweetish and astringent taste. When chewed it imparts a red color to the saliva and may stain the teeth. It is the dried juice of the *Pterocarpus marsupium,* a tree which is found in the eastern coast of India. The term "kino" is also applied to various other dried juices from different parts of the world. The only one of practical importance is the so-called Australian kino, commonly known as red gum, which is derived from various species of eucalyptus trees, especially the *E. rostrata.* Kino is obtained by incising the bark of the tree and catching the juice which exudes in various forms of containers, and dried by exposure to the sun and air. Alcohol dissolves 90 per cent. of it, and water about 80 per cent. It contains in the neighborhood of 60 to 75 per cent. of kinotannic acid, which is closely allied to the tannin found in gambir. This form of tannin is readily oxidized, and solutions of kino on exposure to air very soon become gelatinous and lose their astringency.

Tinctura Kino (5 per cent.)..... 1 to 2 fluidrachms (4–8 mils).

Kino is used chiefly in the treatment of diarrhœa, but occasionally locally as a substitute for tannic acid in sore throat or local hemorrhages.

ACETIC ACID.

Pure acetic acid, or, as it is more commonly known, glacial acetic acid, is a colorless liquid with a characteristic pungent odor, which

solidifies at 59° F. It is obtained by the fermentation of alcoholic liquids and from the dry distillation of wood. Ordinary vinegar contains from 4 to 6 per cent. of acetic acid. The Pharmacopœia recognizes *Acidum aceticum glaciale* (99 per cent.), *Acidum aceticum* (36 per cent.), and *Acidum aceticum dilutum* (6 per cent.).

Acetic acid, when taken internally, is oxidized in the system, its salts appearing as carbonates, and the acetates are valuable for their saline effects. Locally the acid is irritant and astringent. The glacial acetic acid, owing to its property of dissolving gelatin, is mildly caustic, but as a practical escharotic it has been largely replaced by the more active trichloracetic acid. In dilute solution acetic acid is used as an external astringent and styptic. In the form of vinegar it is often useful as an emergency remedy in the treatment of local hemorrhages, especially hæmatemesis; for the latter purpose vinegar may be diluted with equal parts of water and administered in teaspoonful doses at short intervals until the bleeding is controlled. It is also a popular remedy in the treatment of sunburn. On account of its pungent odor acetic acid is sometimes employed instead of smelling salts for the relief of minor syncopes. Frequently the smelling of it will relieve the nausea following etherization.

UNOFFICIAL TANNINS

Chemical ingenuity has brought forward a number of compounds of tannic acid which possess certain advantages over the natural forms of the drug, especially in the treatment of diarrhœas. These compounds are all of them constructed with a purpose of presenting a preparation which shall be insoluble and not affected by the gastric secretions, but shall be decomposed in the intestinal tract with the liberation of active tannic acid. The following may be mentioned as typical of the group:

Tannalbin (*Tannin albuminate*).—This is a light-brown powder, insoluble in water or the gastric juice, but decomposed by the alkaline juices of the intestines with the liberation of its constituents. It is tasteless, odorless, and non-irritant. It is a valuable remedy in the treatment of intestinal catarrh and relaxation requiring the use of an astringent. Dose, twenty to forty grains (1.2–2.5 Gm.).

Tannacol (*Gelatin tannate*).—A tasteless, odorless powder, probably identical in its therapeutic application to tannalbin, although Rosenheim affirms that it is superior in that it is less apt to be affected by the gastric juice, and is of greater uniformity of constitution. Dose, fifteen to thirty grains (1–2 Gm.).

Tannoform.—Commercial tannoform is the condensation product of gallotannic acid and formaldehyde. It is a bulky, pinkish powder, which is believed to be decomposed by the alkaline juices of the intestines setting free tannic acid and formaldehyde, and being, therefore,

both astringent and antiseptic. It has been recommended by numerous practitioners in tuberculous and other diarrhœas in doses of five to fifteen grains (0.3–1 Gm.) three times a day.

It is also a valuable external remedy to arrest excessive sweating, especially in hyperidrosis of the feet, where it probably exercises an antiseptic as well as astringent action.

Tannigen, or diacetyl-tannic acid, is insoluble in the gastric juices, but supposed to be readily dissolved in the intestines, and is recommended as an astringent in diarrhœa in doses of ten to fifteen grains (0.6–1 Gm.).

Protan is defined as a nucleoproteid of tannin containing about 50 per cent. of tannin. Its field of usefulness is the same as that of tannalbin. The dose is 20 to 30 grains (1.2–2 Gm.).

The mineral astringents include the salts of aluminum, copper, zinc, silver, and iron. The last two are considered elsewhere in this work. (See pages 348 and 276.)

ALUMINUM.

Materia Medica.—Aluminum is one of the most widely distributed of the heavy metals. Clay is composed very largely of aluminum silicate, the variety known as kaolin being almost pure aluminum silicate. The oxide of aluminum is the basis of corundum and emery, and the crystallized forms of this salt occur as the precious stones sapphire and ruby. Besides this, the various salts of aluminum are found in many other minerals, as cryolite, feldspar, etc. The U. S. Pharmacopœia recognizes three salts of the metal.

Under the name of alum is official the double sulphate either of aluminum and potassium or of aluminum and ammonia; these are designated respectively as potassium and ammonium alum. They each occur in the form of large, colorless, octahedral crystals, which are often aggregated in large masses. Their taste is astringent, acidulous, and sweetish, and they act as acids, decomposing the carbonates and reddening litmus. When heated they part with their water of crystallization and are converted into a white powder, which is known as dried alum or burnt alum. The potassium alum dissolves in between 7 and 8 parts of water; ammonium alum is somewhat less soluble. Alum is incompatible with all the carbonates and hydroxides, potassium tartrate, and the soluble salts of lead and silver.

Aluminum hydroxide is a white, amorphous, odorless, tasteless, permanent powder, insoluble in water and alcohol, which has been used as a feebly astringent, desiccant powder in inflammatory skin conditions.

Besides these salts which are recognized by the Pharmacopœia, the National Formulary recognizes a solution (*liquor alumini acetatis*) containing a little less than 8 per cent. of basic aluminum acetate, and also a solution of aluminum acetico-tartrate, the latter being of less importance.

Official Preparations:

Alumini Hydroxidum	External use.
Alumen (Alum)	10 to 20 grains (0.6–1.2 Gm.).
Alumen Exsiccatum (Dried Alum)	External use.

Probably all the soluble salts of aluminum are more or less astringent and antiseptic. Alum is one of the most powerful astringents we possess, and in strong solution highly irritant; the dried alum is even mildly caustic. Its germicidal action is relatively feeble. The acetate of aluminum is actively astringent, although probably somewhat less so than alum. It is, however, much less irritant and a much more powerful bactericidal; the solution of aluminum subacetate appears to almost equal phenol in germicidal powers.

Siem has shown that the intravenous injection of soluble salts of aluminum, such as the sodium aluminum tartrate, produces a peculiarly slow form of poisoning, the symptoms sometimes not appearing for as long as two weeks after the injection. There is a progressive loss of weight, and clonic convulsions, and disturbance of sensation all over the body. After death, inflammatory changes are found in the alimentary canal, and fatty degenerations in the kidneys and liver. It has commonly been stated that alum is not absorbable, but in the experiments of Gies considerable proportions of aluminum were recovered from the blood of dogs to whom alum had been administered by the mouth.

Therapeutics.—None of the salts of aluminum are of any value as internal remedies except that alum, being a sulphate, has been used in both acute and chronic lead poisoning, and in the latter is supposed to have some special value in relieving intestinal colic.

Locally the salts of aluminum are not only astringent but also antiseptic, and some of them quite powerfully so. The most popular by far of the official salts is the double sulphate of aluminum and potassium, commonly known as alum. This is a very powerful but somewhat irritant astringent. It was formerly employed in the treatment of various inflammations and congestions of mucous membranes, but is to-day very rarely used for this purpose. Its chief uses at present are for the purpose of hardening the skin, checking excessive sweating, especially of the feet, and as a styptic in local hemorrhages. The dried alum is mildly caustic in its effect.

Aluminum hydroxide, although but little employed, is a valuable sedative astringent in inflammatory conditions of the skin, such as eczemas and burns. It is usually applied in the form of an ointment containing from ten to twenty per cent. of the salt.

The aluminum acetate affords a useful antiseptic and astringent gargle in stomatitis and pharyngitis; for this purpose the National Formulary solution may be diluted with 4 to 8 parts of water. It is also used as a surgical dressing for suppurating ulcers, and externally in sunburn and other forms of dermatitis.

LEAD.

Materia Medica.—There are five salts of lead, exclusive of the plasters, which are recognized by the Pharmacopœia.

Lead acetate or *sugar of lead* occurs in transparent, acicular, often aggregated, crystals, of a sweet, styptic taste. It is soluble in water, to which it usually imparts a slight milkiness. From its solution it is precipitated black by sulphuretted hydrogen, white by soluble carbonates, chlorides, and sulphates, and bright yellow by potassium iodide. It is also incompatible with the mucilage of slippery elm, but scarcely so with that of flaxseed or of pith of sassafras.

The solution of lead subacetate, sometimes known as Goulard's Extract, is made by boiling lead acetate and lead oxide together. It contains twenty-five per cent. of lead subacetate. The approximate formula is $Pb_2O(CH_3COO)_2$. The *liquor plumbi subacetatis dilutum* contains but one per cent. of lead subacetate and is too feeble for any use. Neither of these preparations is used except externally.

Lead oxide or *litharge,* which is prepared by blowing air through melted lead, occurs in small yellowish or orange-colored scales, which are insoluble in water and alcohol, but are soluble in acetic or dilute nitric acid and in a warm solution of the fixed alkalies. It is occasionally used as a desiccant astringent powder for ulcers, but its chief employment in medicine is in the making of *lead plaster,* which consists chiefly of lead oleomargarate. Lead plaster occurs in grayish, cylindrical rolls, which become adhesive at the temperature of the body, and, spread upon kid, is sometimes used as a protective to parts exposed to pressure, or to superficial ulcers or abrasions.

Official Preparations:

Plumbi Acetas	1 to 3 grains (0.06–0.2 Gm.).
Plumbi Oxidum	Not used internally.
Liquor Plumbi Subacetatis [Lead Water; Goulard's Extract]	External use.
Liquor Plumbi Subacetatis Dilutum	External use.
Emplastrum Plumbi	External use.

Therapeutics.—Internally lead, in the form of its acetate, is used at times as an astringent in the treatment of serous diarrhœa, especially in combination with opium. The solution of lead subacetate is very widely used under the name of lead water as an embrocation in various acute inflammatory conditions, as sprains and bruises, more frequently combined with tincture of opium, forming the widely-renowned lead water and laudanum. It is very doubtful whether this highly popular lotion possesses any therapeutic value outside of the alcohol contained in the tincture of opium.

Toxicology.—Acute lead poisoning is usually produced by some soluble salt, and most frequently the acetate, although occasionally large doses of the insoluble salts may give rise to serious acute poison-

ing. When a toxic dose of lead acetate has been ingested the first symptom is usually a persistent, sweet, somewhat metallic taste; this in a few minutes is followed by vomiting, which may or may not be preceded by nausea. The matters vomited are often milky white, from the presence of lead chloride. A severe burning persistent pain in the abdomen now comes on, and is accompanied by a craving for drink. There may be obstinate constipation, or diarrhœa may ensue: in either case the stools are generally black from the sulphide of lead. In certain cases a state of collapse is developed; the pulse falls to forty or fifty per minute, the voice is lost, the face is deadly pale, the lips are livid, and syncope seems imminent. In other instances the nervous symptoms may predominate, or they may accompany those of disordered circulation: cramps in the calves of the legs, severe neuralgic pains in the extremities, paralysis and anæsthesia, vertigo, stupor, may any or all of them be present. In fatal cases, coma, with or without convulsions, finally develops. A distinctive mark of lead poisoning, which occasionally is present very early, is the blue line upon the gums. After death inflammation of the alimentary mucous membrane is sometimes, but not always, found. One ounce of lead acetate, subacetate, or nitrate may take life.

The *treatment* of *acute lead poisoning* consists in the evacuation of the stomach, the exhibition of sodium or magnesium sulphate, and the meeting of the indications as they arise. The Epsom and Glauber's salts act as chemical antidotes, by precipitating the insoluble sulphate of lead, and also, if in excess, empty the bowel of the compound formed. To allay the gastro-intestinal irritation, albuminous drinks should be given and opium freely exhibited.

Chronic lead poisoning is a subject of much medical and economical importance. It is, however, impossible to treat it except in the most cursory manner in a work of this character. It occurs almost always accidentally, and most frequently among those whose occupation exposes them to daily contact with some compound of the metal; manufacturers of white lead, painters, glaziers, and similar artisans furnish the greater number of victims. It may be seen, however, in persons of all conditions of life, for, although neither food nor drink is often purposely adulterated with lead, yet it is frequently introduced into the system accidentally along with those necessities. Lead pipes are habitually used for the conveyance of water, and when the water contains salts of lime, even in minute proportion, no evil results, because through the decomposition which ensues insoluble coatings are deposited on the inside of the pipes.* When the water is pure, no such reactions occurring, the lead is slowly dissolved in the form of a carbonate, and poisoning may result. Poisoning has also frequently resulted from the employment of cosmetics and hair-dyes, from the internal or external medical use of

* For an elaborate article on the chemical relation of water to lead, see *Schmidt's Jahrbücher*, cxliv, 279.

lead preparations, from cooking bread with painted wood, from imperfectly burnt pottery, from habitually biting silk thread which rascally manufacturers treat with lead to give weight to it, from lead bullets retained in the body, from the prolonged therapeutic use of lead, etc., etc. Two types of saturnism are recognized, the first in which the most prominent symptom is intestinal colic associated with constipation, and the other in which there is marked involvement of the nervous system either with or without intestinal disturbances. In the first type, which is sometimes spoken of as subacute, the symptoms generally come on after some days of malaise and wretchedness, or sometimes very suddenly, the victim is taken with abdominal colicky pains, which increase in intensity until they become very severe. They are constant, with occasionally exacerbations, are sometimes dull, sometimes sharp, are generally described as twisting, and seem to center around the umbilicus. Very often there are repeated retching and vomiting. The walls of the abdomen are retracted, rigid, knotted; the bowels are obstinately costive; the tongue is contracted and whitish, the appetite gone, and the thirst sometimes excessive. Neuralgic pains in the thorax and in the extremities are of frequent occurrence. In some cases the conjunctiva is distinctly icteroid. This condition, which is known as *colica pictonum*, or *lead colic*, may after a time abate, and the patient convalesce; more usually, however, the attacks recur from time to time, becoming gradually less severe and distinctive, and the patient gradually passes into chronic lead poisoning. Occasionally the colic increases in severity; sometimes the course of the disease is interrupted by various violent accidents.

In the second form of chronic lead poisoning the abdominal symptoms may or may not be present, but the most marked features are referred to other organs, more commonly to the nervous system. The manifestations of nervous lead intoxications are so protean in their symptomatology as to baffle concise description. It has been said that chronic lead poisoning may simulate any known nervous disease.

By far the most common nervous manifestations of plumbism seen in this country consist of failure of health, more or less digestive disturbance, and double wrist-drop—*i.e.*, paralysis of the extensor muscles of each hand. Not rarely, the only noticeable symptom is the wrist-drop, the general health seeming to be very good. The true nature of such cases can usually be at once recognized by the bilateral character of the wrist-drop, cerebral and pressure paralyses being almost invariably unilateral. But cases of bilateral pressure palsy have been noted as well as occasional ones of unilateral plumbic wrist-drop, due to a local absorption of lead, in artisans who had one hand much of the time in a preparation of the metal. Cases of this kind have been recorded by Manouvriez. The wrist-drop may exist alone, but not rarely there is with it anæsthesia of the affected part, or sometimes of the shoulders or other unparalyzed portion of the body.

When the paralysis is complete, the electro-contractility of the muscles is in great part or altogether absent.

Another group of cases present symptoms resembling those of anterior poliomyelitis. These cases may generally be diagnosed from the infectious myelitis by the involvement of the bladder and rectum and the presence of violent neuralgic pains. Other cases have shown symptoms suggesting those of delirium tremens and of various metabolic disturbances, such as gout; neuritis may be found in almost any nerve or simultaneously in several nerves.

As any of the obscure manifestations of lead poisoning may exist, and even prove fatal, without distinct history of other more characteristic phenomena, great care is sometimes necessary to avoid being misled, and not rarely the true nature of saturnine epilepsy or of saturnine albuminuria is overlooked. The symptoms which are sufficiently characteristic to be of diagnostic value in chronic lead poisoning are the peculiar colic, the blue line upon the gums, basophilic granulation of the red blood-corpuscles, and the appearance of lead in the urine. No one of these symptoms, however, can be completely relied upon. The blue line on the gums—which may be simply small spots of pigmentation at the very edge of the gingival margin or may form a continuous line around several teeth—is quite characteristic of the poisoning. It is probable that this discoloration is due to the formation of lead sulphide in the walls of the capillary, and chronic lead poisoning may exist without this blue line, especially in persons who are attentive to mouth hygiene. The basophilic granulation of the red blood-corpuscles may occasionally be observed in other conditions, but rarely to the extent found in saturnism, but, according to Hamilton, its absence is of little value in excluding this condition. In every case suspected of lead poisoning, or, indeed, one might almost say in any atypical case of nervous disease, it is well to have the urine examined for lead. The finding of lead, however, in the excretion is no proof that the symptoms are due to the metal. Generally there is an elevation in the blood-pressure due to spasm of the arterioles. According to Deroide and Le Compt, the urine of saturnine patients universally contains hæmatoporphyrin, which can be recognized by the spectroscope.

The symptoms of chronic lead poisoning are probably in great part secondary to the structural alteration produced by the drug, lead being a poison to all forms of protoplasm. Why in one case one set of organs should be attacked and in another case a different portion of the body is a mystery.

The evidence at present indicates that lead is capable of producing a peripheral neuritis, and also a centric poliomyelitis, which may or may not coexist in an individual case; the probabilities being in favor of a peculiar peripheral neuritis as the primary lesion of ordinary plumbic wrist-drop (see paper by Schultze, also Prevost and Binet). Hemorrhages into the nerve-centers sometimes occur. There seems to be no doubt that lead really affects the nutrition of almost all of the

higher tissues. In saturnine encephalopathy changes have been found in the ganglionic cells as well as in the neuroglia, with stenosis of capillaries and general shrinkage of the cortex. Marked alterations are not rare in the kidneys and other glandular organs, and general fibrosis of the blood-vessels is probably more or less developed in every slowly fatal case of chronic poisoning.

The *treatment* of chronic lead poisoning evidently arranges itself under three indications: first, to prevent the ingestion of more of the poison; second, to aid in the elimination of that in the system; third, to relieve symptoms and restore lost functions.

For the prevention of the absorption, the only problem which presents any difficulty is to find out the source of the poisoning. This, however, as intimated above, although it is most commonly from some occupation, may sometimes baffle the ingenuity of a Sherlock Holmes.

In eliminating the lead it is essential, first to see that the bowels are thoroughly opened in order not only to prevent the absorption of any lead which may be stored up in the intestines, but also to facilitate the excretion through the glands of the bowel. For this purpose the only cathartics which should be considered are the sulphates, either of sodium or magnesia, because they not only increase the secretions of the intestinal glands, but also because they are chemical antidotes, precipitating the lead as a highly insoluble sulphate. After the bowels are working freely, efforts should be made to increase the elimination of the poison through other channels. The most valuable remedy for this purpose is potassium iodide, which seems to form in the body a double salt with lead, similar to the salt formed with mercury. Oddo and Silbert assert that the elimination through the skin can be greatly hastened by free sweating through the conjoint use of hot baths and pilocarpine. I have seen life apparently saved by venesection and infusion of physiological salt solution in a case of saturnine cerebritis.

The treatment of the third indication—that is, the relief of symptoms—of course will vary according to what special type of lead poisoning we are dealing with. In the lead colic the most valuable symptomatic remedy we have is belladonna, or allied drug. Atropine has been shown to possess the property of overcoming intestinal spasms even when given in doses too small to exert any action upon the normal intestines. Opium is also sometimes of service for this purpose, but its value is greatly lessened by its tendency to constipate. In cases where the symptoms are those of peripheral neuritis, such as in the wrist-drop, the most valuable method of treatment is electricity, which should be persisted in even although at first it gives no apparent benefit. In nearly all the cases in which there is involvement of the nervous system, but especially in those types which resemble poliomyelitis, strychnine in full doses should be employed.

ZINC.

The salts of zinc are most of them astringent and antiseptic, the soluble ones powerfully so, the less soluble feebly so. The United States Pharmacopœia recognizes besides the metal ten salts and three preparations, of which three are of possible therapeutic value.

Materia Medica.—*Zinc sulphate,* or *white vitriol,* occurs in irregular white masses, the *pure* zinc sulphate in minute, transparent, four-sided, prismatic crystals, which effloresce slightly in dry air, and are soluble in 0.53 part of water at 77° F. and in 0.2 part of boiling water, also soluble in about three parts of glycerine; insoluble in alcohol. The taste is styptic and peculiar.

Zinc oxide is a white or yellowish-white powder, insoluble in water or alcohol, but soluble without effervescence in dilute acids.

Precipitated zinc carbonate is intended to replace the old impure native carbonate, calamine, and is made by precipitating zinc sulphate with sodium carbonate. As the greatest virtue of calamine was its pink color, and as the pure carbonate is white, this refinement of chemistry hardly constitutes an important advance in practical therapeutics.

Zinc acetate occurs in white, micaceous crystals, which effloresce in a dry atmosphere and are very soluble in water. The taste is astringent and metallic. The zinc acetate resembles in its physiological and therapeutic qualities the sulphate, but is probably somewhat less active.

Zinc chloride occurs in white or nearly white porcelain-like masses freely soluble in water. It is used as a caustic and disinfectant.

Zinc phenolsulphonate, sulphocarbolate of zinc, occurs as efflorescent, colorless crystals, freely soluble in water. It is largely used as an intestinal antiseptic, but is probably of no value.

Zinc stearate is a white powder with a slight fatty odor, insoluble in water, alcohol, or ether. It is used as a dusting powder in similar conditions to those calling for zinc oxide.

Official Preparations:

Zincum	Not used internally.
Zinci Acetas	2 grains (0.12 Gm.).
Zinci Carbonas Precipitatus	External use.
Zinci Chloridum	External use.
Zinci Oxidum	2 grains (0.12 Gm.).
Zinci Phenolsulphonas	2 grains (0.12 Gm.).
Zinci Stearas	External use.
Zinci Sulphas	As an emetic 15 to 30 grains (1–2 Gm.).
Zinci Valeras	3 grains (0.2 Gm.).
Unguentum Zinci Oxidi (20 per cent.)	External use.
Liquor Zinci Chloridi (50 per cent.)	Not used internally.

Zinc, when introduced into the general system, exercises a marked influence upon the central nervous system, which is, however, not clearly understood. It is possible that it acts as a depressant to

the spinal cord and also to the voluntary muscles. Neither our knowledge of its physiological effects nor clinical experience affords any justification for the internal use of the metal.

Therapeutic Uses.—The most widely employed of all the salts of zinc is the oxide, which is highly prized for its sedative and astringent effects in various inflammatory conditions of the skin, especially in the form of the official ointment, popularly known as "zinc ointment." It has also been used as an astringent in chronic catarrhal diarrhœa and for the treatment of certain nervous conditions as epilepsy and chorea, although its value for the latter purposes is doubtful, to say the least.

Zinc sulphate is much more actively astringent, but its most important use in medicine is as a rapidly acting emetic, being one of the safest and most certain of all this class of remedies. It is especially employed in the treatment of cases of poisoning in doses ordinarily of thirty grains.

COPPER.

The only official salt of copper is the sulphate. This occurs in blue, transparent, slightly efflorescent, rhomboidal prisms, or their fragments. It dissolves, at 77° F., in about 2.2 parts of water and in 0.5 part of boiling water; almost insoluble in alcohol. With ammonia its solution precipitates a bluish-white cupric hydrate, which redissolves when an excess of the alkali is added, forming a rich deep blue solution.

Physiological Action.—In very dilute solution the copper sulphate acts locally as a stimulant and mild astringent; in a more concentrated form it is an irritant; in powder it is a mild caustic, but scarcely capable of destroying sound tissue.

Copper has a destructive influence on certain of the lower forms of vegetable life, such as the fresh-water algæ and the bacillus of typhoid fever, even when present in extraordinarily minute proportions. Thus Gildersleeve found that copper sulphate in the proportion of one part in one million is sufficient to kill all typhoid germs in three hours, although other micro-organisms were more resistant, and Stewart found that water inoculated with typhoid bacillus and kept in copper vessels contained none of these organisms after three hours. When large amounts of foreign matter are present in the water, however, the germicidal powers of copper are so greatly reduced that it is doubtful whether the metal is of any practical value.

According to Falk, copper sulphate causes in the lower animals great depression of temperature, with a progressive paralysis and death finally from respiratory failure.

Therapeutic Uses.—Copper is used in medicine purely for its local effects. As an astringent it is occasionally employed in chronic enteritis, but much more frequently it is used as a local astringent and caustic in the treatment of small ulcers, especially of the conjunctiva. It is a powerful and certain emetic, although not so gen-

erally useful as the zinc sulphate, because of greater danger of undue irritation of the mucous membrane of the stomach. Its emetic action is purely local. Because of its combining with phosphorus to form a copper phosphide, being thereby antidotal as well as emetic, it is the remedy of choice for emptying the stomach in phosphorus poisoning.

Poisoning.—Copper sulphate in overdose may give rise to an acute gastro-enteritis of great severity. The symptoms are violent vomiting and purging, with severe colicky pains and in some cases evidence of great nervous disturbance, as shown by convulsions, paralysis, delirium, or anæsthesia. In many cases violent nephritis and even hæmaglobinuria have been noted. The matters vomited are greenish or bluish. The most efficient chemical antidote is the yellow prussiate of potassium (potassium ferrocyanide), but in its absence, as it is necessary that an antidote be administered immediately if it is to be of any service, albuminous matters, as the whites of eggs or milk, and even soap, are of some utility.

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CHAPTER III.

NERVOUS SYSTEM.

SOMNIFACIENTS.

There appear to be at least three distinct sorts of intellectual activity in the cerebrum. There is the perceptive faculty, by which we appreciate the influence of impulses upon the nerves of sensation and pain as well as those of the special senses; there is the so-called psychomotor function, which originates the impulses for volitional movement, and, finally, there is the sphere of purely intellectual activity, in which apparently originate and flow those forms of impulses which are manifest only subjectively as thoughts. These three divisions of cerebral or mental activity have quite distinct pharmacologic relations; some drugs act much more powerfully on the perceptive centers, others affect solely the motor area, and there is a group of drugs whose predominant effect is a depression of the purely intellectual centers. This last group constitute the true somnifacients or hypnotics. Although under special conditions there are other drugs which are clinically useful to produce sleep—for instance, in the presence of severe pain—all of the true somnifacients belong chemically to the methane homologues or open-chain carbon compounds.

From the work of Meyer and of Overton it would seem that all these narcotics are characterized by a greater solubility in fatty vehicles, especially the lipoids of the nervous system, than in water, and it is probable that their physiological effects are in some way dependent upon this physical property. It is evident that, as the central nervous system is composed very largely of substances allied to the fats, any agent which dissolves by preference in oils rather than water will be taken up from the blood stream as it passes through the nerve-centers and thereby tend to accumulate in the central nervous system.

The narcotics of this group separate themselves sharply from other sleep-producing substances in the relative feebleness of their action on other portions of the body; for instance, morphine is, in sufficient doses, a powerful hypnotic, but the quantity required to produce sleep has a marked effect upon glandular secretions and upon the circulation, whereas the methane homologues produce apparently little change in the bodily functions which cannot be attributed to their effects upon the brain. There is, moreover, a close similarity, speaking physiologically, between all the narcotics of the aliphatic series.

It seems to be a universal tendency of the open-chain compounds to depress the central nervous system. It must not be understood, however, that all of the derivatives of this group are narcotics. So

far as known, none of the acids are sleep producing, and most of the aldehydes are oxidized in the body into their corresponding acids and, therefore, possess no hypnotic power; further, the introduction of several hydroxyl groups, as in the polyatomic alcohols, destroys the narcotic effects, otherwise the sugars would be narcotic instead of nutrient. Generally speaking, the introduction of a halogen, especially chlorine, into their molecule seems to enhance the narcotic power; for instance, ethyl chloride is a more actively depressant than ethyl oxide (ether).

All of the drugs of this series affect all portions of the central nervous system, acting upon it in inverse order of its development; thus the first portion affected is the intellectual centers in the brain, after the cerebrum is paralyzed, then the reflex centers in the spinal cord, and finally, if sufficient be administered, the vital centers in the medulla. The precise field of usefulness as well as the relative safety of the individual members of these narcotics will evidently depend upon the ratio between the dose required to affect the brain and that which would paralyze the lower neuron. If the difference between the cerebral depressant and medullary depressant dose be small it is evident that the drug would be so dangerous as to preclude its usefulness. If the gap between spinal and medullary depression be larger than that between brain and cord, then the drug becomes useful not only as a sleep-producing agent but also for the purpose of quieting convulsions.

The clinically useful somnifacients may be divided into four groups: (1) Simple aliphatic compounds (paraldehyde), (2) those containing a chlorine atom (chloral hydrate and chloralformamid, (3) those containing a carbamic ester (urethane and veronal), (4) those containing ethyl-sulphonic radicals (sulphonmethane and sulphonethylmethane).

PARALDEHYDE.

Materia Medica.—This substance, which is a polymer of acetaldehyde $(CH_3COH)_3$, occurs as a colorless liquid, with a strong and disagreeable odor and a burning taste. It is soluble in eight parts of cool water, less soluble in warm water, and mixes in any proportions with alcohol or ether.

Paraldehydum .....½ to 1 fluidrachm (2–4 mils).

Physiological Action.—Paraldehyde is absorbed rapidly through mucous membranes, its effect after oral administration usually being evident within ten to twenty minutes. Its elimination is also rapid, but frequently enough will remain in the system for many hours after its administration to give an odor to the breath. It escapes from the body unchanged, in part through the lungs and in part through the kidneys.

In moderate doses paraldehyde appears to have little or no direct

action upon any organ save the brain, of which it depresses the centers of consciousness, producing a sleep in its manifestations indistinguishable from normal sleep. In larger quantities there is evidence of a depressing action upon the lower nerve-centers, as is shown by diminished reflexes. Although toxic doses of paraldehyde will produce a condition of coma with loss of sensation, the therapeutic dose has no analgesic effect.

As a result of the sleep produced by it, there is a lessening in the nitrogenous metabolism, with a slight fall in temperature.

Therapeutic Uses.—Although somewhat less powerful in its hypnotic effect than chloral hydrate, it is a very valuable somnifacient where a rapid action is desired, and is especially serviceable because of its lack of any direct action upon the circulation.

It is best administered dissolved in some aromatic water. Unless well diluted it may irritate the stomach. Its most serious disadvantage is the unpleasant odor it imparts to the breath.

HYDRATED CHLORAL.

Materia Medica.—Chloral, or trichloraldehyde ($CCl_3.CHO$), which is itself not used in medicine, is an oily liquid giving off, at ordinary temperatures, pungent fumes: it is made by the action of chlorine on alcohol. It unites with one molecule of water to form a hydrate.

This hydrated chloral is a slightly volatile, crystalline solid, of a hot burning taste, freely soluble in water, ether, and alcohol. It usually occurs as transparent, colorless tablets, but sometimes in acicular or rhomboidal crystals.

Incompatibilities.—Chloral hydrate is decomposed by the alkalies and alkaline carbonates, breaking up into chloroform and formic acid. When rubbed up with molecular portions of certain members of the aromatic series, as phenol, camphor, or menthol, it liquefies; it is probable, however, that this change is a purely physical one, not chemical. In strong alcohol it gives up its molecule of water to form a chloral alcoholate; the presence of certain salts, as sodium bromide, accelerates this change.

Chloralum Hydratum .....10 to 20 grains (0.6–1.3 Gm.).

Physiological Action.—Hydrated chloral is absorbed with great rapidity, its action being often manifested within five minutes after its ingestion. It circulates through the body as chloral; its exact fate in the system has not been determined, but it escapes in part in the form of a copper-reducing substance, urochloralic acid, and probably in part unchanged.

Nervous System.—The most constant and prominent of all the symptoms produced by moderate doses of hydrated chloral is sleep, due to a direct depressant action upon the higher cerebral centers. The drug seems also to affect the psychomotor area, but sensation is

not affected except after toxic doses; in the milder degrees of this sleep there is no anæsthesia.

The introduction of a chlorine atom into the molecule of an aliphatic narcotic increases its depressant action upon the whole central nervous system, but disproportionately upon the lower neuron. Chloral hydrate is, therefore, not only one of the most powerful somnifacients of this group, but also exercises a marked influence on the centers in the spinal cord and in the medulla.

When administered to a frog in sufficient dose chloral produces a condition of complete paralysis, with muscular relaxation and entire absence of all reflexes. Electrical stimulation of the sciatic nerve will in such a frog give a perfectly normal response in the supplied muscle, showing that the drug has affected neither the conductivity of the nerve-trunks nor the contractility of the muscle substance. Since there is entire abolition of reflexes, it is evident that the action must have been below the brain, either upon the sensory or motor ganglia of the spinal cord. The loss of voluntary movement shows that there is an interruption in the motor pathway rather than in the sensory apparatus, and we conclude, therefore, that the paralyzing action of chloral hydrate must be upon the motor centers of the spinal cord. In both the frog and the mammal doses of chloral too small to cause complete paralysis reduce the irritability of the reflex centers directly in proportion to the dose employed. The influence upon the spinal cord is easily demonstrable in human beings.

While the medulla is somewhat more resistant to the action of chloral than the spinal cord, evidence of an influence upon the medullary centers is seen in cases of chloral poisoning in the reduction in the frequency as well as the depth of the respiration. Although the breathing is slowed by therapeutic doses it is generally not lessened in depth; this reduction in the respiratory rate is due not to a direct action upon the medulla, but is simply a result of the sleep produced by the drug. The other centers in the medulla, notably the vasomotor, are also more or less depressed by large doses of chloral.

Circulation.—Although the effects of hydrated chloral upon the circulation are subsidiary to its action upon the central nervous system, and usually not manifested from the hypnotic use of the remedy, in sufficient quantities it produces a marked fall of the blood-pressure, generally with a slowing of the pulse.

The slowing of the heart is not prevented either by previous section of the pneumogastric nerves or by the administration of atropine, and is, therefore, not caused by an effect upon the inhibitory mechanism. It is apparently attributable to a reduction in the irritability of the heart muscle.

The lowering of the blood-pressure produced by chloral is the result of a simultaneous diminution in the output of the heart and of a widening of the blood-vessels. The diminished work of the heart is due not merely to the slowing of the rate, but also to a weakening

of the cardiac vigor. Apparently in some cases the heart muscle is more than ordinarily susceptible to chloral, and instances of sudden heart-failure from its use are not unknown.

The dilatation of the blood-vessels by chloral is brought about primarily by an action upon the vasomotor centers in the medulla, although if the dose be sufficiently large there is later also a direct paralysis of the arterial walls. Although the effect upon the heart is seen comparatively early in chloral poisoning, vasomotor paralysis is generally complete before heart paralysis, so that late in chloral poisoning, in the lower animals, there is a stage in which, while the heart is beating with enough force to maintain a sufficient pressure to be compatible with life, the blood-vessels are completely relaxed and the ordinary vasomotor stimuli, as asphyxiation, will not cause an elevation of the blood-pressure.

Metabolism.—Large doses of chloral have been shown to reduce very markedly the elimination of carbonic acid and to produce a fall in the bodily temperature. This change in metabolism is probably due, however, simply to the marked quietude it produces. Peiser affirms that the prolonged use of chloral produces similar degenerations of the albuminous tissue that are seen after chloroform anæsthesia. (See page 109.)

Therapeutic Uses.—Chloral is useful, clinically, for its action upon the brain, to produce sleep, and upon the spinal cord, for the relief of convulsions.

In insomnias of the nervous type, such as those which result from functional over-excitement of the brain due to excessive mental strain, or from anxiety or other kindred cause, hydrated chloral is, probably, the most certain of the hypnotics. On the other hand, when severe pain causes wakefulness, it is of very little value—at least, in doses which are safe. It is especially in the very obstinate forms of sleeplessness, such as those seen in delirium tremens and certain types of insanity, that the certainty of effect makes chloral hydrate peculiarly valuable. It must not be forgotten, however, that whenever there is a weakness of the heart chloral hydrate is a treacherous remedy, and in patients with cardiac lesions, especially muscular degenerations, great caution must be exercised in its administration. Under such circumstances the dose of fifteen grains should never be exceeded, nor repeated more than once, unless after an interval of several hours. It is also frequently employed in the milder types of insomnia, such as that which is seen during convalescence from acute fevers, but usually is in these cases no advantage over the less powerful but safer hypnotics.

The second indication to meet which hydrated chloral may be employed is to relax spasm. Because it acts on the motor side of the spinal cord hydrated chloral controls all types of convulsions, whether of cerebral or spinal origin. It must be remembered, however, that its action in most of these conditions is only that of a palliative, merely

to prevent the results of the convulsion itself, not to relieve the underlying condition. The question of whether or not to use it in any individual case is answered not upon the character of the convulsion, but upon the severity of it. If the patient's life is immediately endangered by the convulsions, hydrated chloral is strongly indicated. Thus in tetanus it is one of the most valuable agents we have, but must be given boldly and at short intervals. Although it has no curative effect in chorea, it is useful in those cases in which speedy death is threatened from incessant and violent movements, or in cases where a temporary lull is of importance, as when complicated with a fracture. It is also of service in puerperal and uræmic convulsions, and has been employed in status epilepticus to interrupt the succession of spasms. In strychnia poisoning the promptness of its effect makes it of peculiar value.

In many of the spasmodic affections of childhood it has been employed with apparent good; in singultus, in spasmodic nocturnal enuresis, in laryngismus stridulus, and in whooping-cough it may be tried as a temporary symptom reliever. In spasmodic disorder, when it is desired temporarily to suppress the motor disturbance, chloral remains the standard remedy.

Locally, chloral is sometimes used as a stimulant anodyne; the combination of equal parts of chloral, menthol, and camphor makes a very useful liniment in cases of neuralgia. It was at one time used for its antiseptic effect in bed-sores, inoperable cancers, and other foul ulcers; for this purpose, however, it has largely passed out of vogue.

Toxicology.—The most prominent symptom of chloral poisoning is deep sleep, from which, in the milder degrees, the patient can be awakened, but when left to himself immediately falls again into a state of somnolency. In this stage the pulse is somewhat slow, the pupil slightly contracted, the respiration slow but full and regular. In severe poisoning the sleep deepens into a profound coma, the pulse becomes feeble and rapid, respirations slow and shallow, the pupil dilated, the reflexes diminished. There is muscular relaxation and sometimes anæsthesia; the skin is cool and moist and pale. There is marked fall of the bodily temperature. Death, if it occur, is usually due to respiratory failure, but in some cases sudden heart-failure has occurred.

There is no chemical antidote to chloral. The stomach should be washed out, preferably with a stomach-tube, as emetics frequently fail to act. To maintain the circulation, digitalis, strychnia, and ammonia may be given hypodermically, and whiskey by the mouth. The bodily temperature should be maintained by the use of external heat. Measures should be adopted to keep the patient awake, on account of the greater activity of the respiratory centers during wakefulness. In preventing sleep those measures which throw an added strain upon the heart, as walking up and down, should be avoided;

the most efficacious means is the use of the electric brush. As a respiratory stimulant strychnia stands pre-eminent; atropine and cocaine are useful as adjuvants.

Thirty grains of chloral have produced death, but Eshleman has reported recovery following the ingestion of 460 grains. There are no characteristic postmortem lesions.

Chloralamid.—Besides the official chloral hydrate, there are other allied compounds which are used in medicine. The chloralformamid ($CCl_3.CH(OH)NH.COH$) was formerly recognized by the U. S. Pharmacopœia. It occurs as odorless crystals with a slightly bitter taste, soluble in 19 parts of water and freely soluble in alcohol.

In this compound the depressant effects of the chloral are more or less overcome by the stimulating action of formamid. In the system the drug is broken up with the slow liberation of chloral. It is slower and less dangerous than chloral hydrate, but is much less efficacious. In the milder forms of insomnia it is often a useful drug in doses of 15 to 45 grains (1 to 3 Gm.).

Isopral.—This is the trichlor-isopropyl-alcohol ($CCl_3CH.OH.CH_3$). It is a somewhat volatile crystalline substance with a faint camphoraceous odor, sparingly soluble in water. Weight for weight, it is a more powerful agent than chloral hydrate, which it seems to resemble closely in its general effects. As, however, it is also more toxic than chloral, it does not appear to be any safer. The dose is from 10 to 20 grains (0.6 to 1.3 Gm.).

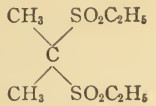
Chloretone.—This substance, known also as acetone-chloroform or chlorbutanol, is trichlor-tertiary-butyl-alcohol ($CCl_3C(OH)(CH_3).CH_3$). It is a crystalline compound with a camphor-like odor, practically insoluble in water, but soluble in alcohol and the fixed oils. It has a marked local anæsthetic action and also some antiseptic virtues. Even in extremely large dose it has very little influence upon the circulation or respiration. As a practical hypnotic it has shown itself an uncertain remedy. It is used locally for its antiseptic and anæsthetic powers, and to some extent internally as a general nerve sedative. Chloretone is a valuable agent in the physiological laboratory as a general anæsthetic; it is possible to produce in a dog anæsthesia of several hours' duration from a single dose. The ordinary dose for human beings is from 10 to 20 grains (0.6 to 1.3 Gm.).

SULPHONES.

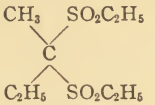
A series of hypnotic drugs were discovered by Baumann which are methane derivatives containing two ethyl-sulphonic—$SO_2(C_2H_5)$—radicals. Of these, two are recognized by the United States Pharmacopœia—sulphonmethane and sulphonethylmethane.

Sulphonmethane, or sulphonal, is made by oxidizing mercaptol by means of potassium permanganate, and occurs in the form of colorless, odorless, tasteless crystals, practically insoluble in cold water,

sparingly soluble in alcohol, but dissolving in fifteen times their weight of boiling water. It is diethylsulphone-dimethylmethane.



Sulphonal.



Trional.

Sulphonethylmethane (trional) differs chemically in that one methyl group has been replaced by an ethyl. Another compound in which both methyls are replaced by ethyls has been prepared and used to a certain extent under the name of tetronal. It is, however, very little employed in this country, and is not recognized by the United States Pharmacopœia.

Sulphonethylmethane is somewhat less insoluble than sulphonmethane, dissolving in 195 parts of water at 77° F., and readily soluble in both alcohol and ether.

Sulphonmethanum .....20 to 40 grains (1.3–2.5 Gm.).
Sulphonethylmethanum .....10 to 30 grains (0.7–2.0 Gm.).

Therapeutics.—Outside of their influence upon the brain and some slight depressant action upon the motor cord, these compounds seem to be almost without effect upon the system. Owing to their slight solubility they are absorbed with great slowness, requiring from one to two hours to produce their effects, and act with great persistency, so that at times, especially after the exhibition of sulphonmethane, drowsiness is manifested the next day. They escape from the body chiefly in the form of ethyl-sulphonic acid.

The original statements of Baumann and Kast that the hypnotic power of these substances is in proportion to the number of ethyl radicals seem to be correct, for the corresponding methyl-sulphone derivatives are without hypnotic power, and trional, containing three ethyl radicals, is more active as a hypnotic than the sulphonal, which contains but two. Because, being less insoluble than sulphonmethane, it acts somewhat less slowly, and because it is more certain and much less likely to give rise to toxic manifestations, the sulphonethylmethane should generally be given the preference.

The sulphones are valuable hypnotics, having, however, little or no analgesic effects. Sleep usually develops in from a half to one hour after the dose, in most cases gradually, but sometimes with abruptness. It is usually quiet, and not followed by any disagreeable after-effects, although sometimes mental confusion and lassitude remain during the following day; these after-results being especially likely to occur in cases in which there is a distinct depression of the brain-nutrition. In the insomnia due to pain they are of little service. For some reason in heart-disease they have not proven safe remedies.

The action of sulphonal upon the reflexes would indicate its em-

ployment in spasmodic diseases, and it has been used with asserted good results in epilepsy, hiccough, chorea, and nocturnal cramps. It has also been commended as a sexual sedative in chordee and spermatorrhœa. It is asserted that it is a useful remedy in colliquative night-sweats.

These drugs should be administered in the form of a powder enclosed in a capsule, or, preferably, stirred up in a glass of hot milk or water immediately before taking. They should never be administered in tablets or pills. Because of the danger of chronic poisoning it should be an invariable rule when administering them for long periods of time to suspend their employment every couple of weeks for a few days to allow the system to clear itself of accumulated drug; the urine should also be carefully watched for the first appearance of a pinkish tint, which should be the signal for immediate withdrawal.

Toxicology.—Dangerous poisoning from a single dose of either of the sulphones is extremely rare, probably on account of their slow absorption; as much as 100 grammes (3 ounces) has been recovered from. On the other hand, the statement that acute sulphonal poisoning never ends fatally is not true, there being at least two cases on record. When, however, the sulphones are taken regularly over long periods of time they frequently give rise to severe grade of chronic intoxication. Sulphonal is not only much more likely to cause poisoning, but the condition is peculiarly fatal.

Although prodromic symptoms probably always usher in chronic sulphone poisoning, they are so slight and so lacking in anything characteristic that in a large majority of cases the condition appears to develop abruptly and, notwithstanding the suspension of the remedy, continues to the fatal issue, death occurring in about seventy-five per cent. of the cases of sulphonal poisoning. The first manifestations are increasing lassitude and weakness, nausea, and gastro-intestinal disturbance, as shown by diarrhœa or constipation. Ordinarily the first symptom noted is the pink coloration of the urine, which deepens until the fluid becomes of a dark-red color, staining the linen upon which it falls. Usually this coloration of the urine is soon followed by obstinate constipation, violent vomiting, spasm of the abdominal muscles and tenderness upon pressure in the region of the liver and stomach, and ordinarily insomnia. At the same time there develop ataxia, suppression of perspiration, paresis of the upper extremities or perchance of irregular groups of muscles, pronounced weakness of the legs, loss of the patellar and other reflexes, paræsthesia, muscular spasms, and finally a condition of profound collapse, with albuminous, hemorrhagic, or suppressed urine, ending in death. After death widespread fatty degeneration, involving in some cases the heart, but especially affecting the liver and kidney, has been found.

In some cases the renal changes have been confined to a glomerular or cortical nephritis, with or without hemorrhage; in other instances the destruction of the kidney has been more complete. Probably the

most characteristic symptom is the appearance of hematoporphyrin, which is the cause of the red coloration, in the urine; its recognition is best made with the spectroscope.

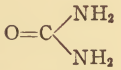
In the treatment of chronic sulphone poisoning the most important measure is to see that the bowels are thoroughly opened and cleaned of any undissolved drug which may be lying there and by slow absorption making the patient's condition continually more hopeless. For this purpose heroic measures are often necessary, and vital time should not be lost experimenting with the milder cathartics. After this the poison should be diluted and elimination encouraged by the free use of water. This may best be given by hypodermoclysis of physiological salt solution as well as by the ingestion of water by mouth. The use of the alkaline carbonates as suggested by Muller is probably also of service. For the heart-failure and other symptoms the appropriate drugs should be administered, but they usually have very little effect.

ETHYL CARBAMATE.

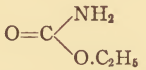
By uniting various of the methane homologues with urea there have been formed a series of esters of carbamic acid which are commonly known as urethanes. Of these the only one official is ethyl urethane, but several others have been employed in medicine.

Ethyl carbamate, or urethane, is obtained by acting upon urea with ethyl alcohol. It occurs in the form of odorless, colorless crystals, having a cooling saline taste. It is soluble in an equal weight of either water or alcohol, also freely soluble in ether, chloroform, and glycerine.

Its relation to urea is shown in the following formulas:



Urea.



Ethyl Carbamate.

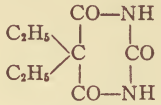
Æthylis carbamas ..... 15 to 45 grains.

Therapeutics.—In ethyl carbamate the depressant effect of the ethyl on the medulla is almost exactly balanced by the stimulating carbamic radical, so that the drug exercises, even in very large doses, almost no influence upon the circulation. It is slightly depressant to the motor side of the spinal cord.

Urethane is without a doubt one of the safest of all the somnifacients. Unfortunately, however, it is less certain in its effects than some of the other narcotics of the series. Its action is prompt and not very persistent. In persons of feeble constitution, because of its safety it should certainly be given a trial. When used freely it is likely to exercise some diuretic effect, because of its decomposition in the body and the liberation of urea.

VERONAL.

Under the trade name of veronal is used the diethyl-barbituric acid, a condensation product of urea and diethyl-malonic acid; it is chemically related to the urethanes.



Veronal.

Veronal occurs as a white crystalline powder, with a slightly bitter taste, very sparingly soluble in water. The sodium salt of diethyl-barbituric acid, which is used chiefly under the trade name of medinal, is soluble in about six times its weight of water.

Physiological Action.—Veronal is absorbed from the alimentary tract somewhat slowly, so that its effects are generally not manifest for half an hour or more after its administration. After small doses it is eliminated almost completely through the kidneys within twelve hours, although a small proportion is probably destroyed in the system. After large doses about half of the quantity administered can be recovered from the urine within twenty-four hours. It is probable that a considerable amount of the other fifty per cent. is destroyed in the system, but Fisher and Hoppe have shown that where large doses are employed repeatedly, there is a tendency of the drug to accumulate in the system; in one case in which 0.5 Gm. was given daily for five days, the drug was not eliminated until four days after the last dose.

In the lower animals it produces ataxia and sleep, and in somewhat larger doses lowers the blood-pressure by dilating the abdominal vessels. The reflexes and the sensory system are not affected by small quantities but may be paralyzed if the dose be sufficient.

Therapeutic Uses.—Clinically veronal has been used to an enormous extent and has proven a reliable somnifacient and, if used with discretion, relatively safe. It is not, however, so completely innocuous as has been, in some quarters, believed.

Veronal is useful as a somnifacient in the milder degrees of insomnia, being probably somewhat more certain in its action than the official urethane. In the more obstinate types of sleeplessness, however, it is not always successful, and, according to Leyden, when the dose is increased there is not a corresponding augmentation of hypnotic power, but the occurrence of unpleasant effects, such as nausea, chilliness, and irregular heart action. Veronal has also been used in epilepsy, hyperemesis, and whooping-cough, but its value in these conditions is still problematical.

Veronal is a rather slowly acting hypnotic, its hypnotic influence beginning ordinarily in about half an hour after its administration. Because of its sparing solubility veronal should never be given in the form of pills or tablets. It may be administered in powder form enclosed in capsules or, better, dissolved in hot water. It should not be

used in patients suffering from either nephritis or cardiac lesions and only with the utmost caution in the aged.

The dose is ordinarily from five to ten grains (0.3–0.7 Gm.).

Toxicology.—Veronal must be ranked among the treacherous somnifacients. The number of serious and fatal cases of poisoning is so large that great care should be employed in its use. Death has been reported in one case from as low as fifteen grains (Wilcox), in another from sixty grains, while alarming symptoms have been produced by even smaller quantities. According of Roemer, the fatal dose for the rabbit corresponds to about forty grains for a man.

In the more serious group of cases there has been a profound coma, the pupils are usually moderately dilated and fixed, the reflexes abolished, the bodily temperature usually reduced, although in some instances there has been a high degree of fever.

In another group of cases the symptoms have been chiefly those of dermal irritation. Ormsby reports a case of a woman who took five grains nightly for five days and developed a violent dermatitis, resembling erysipelas, with a temperature which rose as high as 106° with delirium, followed after six days with desquamation. A number of similar but less violent cases have been reported.

The treatment of veronal poisoning is purely symptomatic.

BROMURAL.

Bromural is a monobrom-isovaleryl-urea. It occurs as colorless crystals freely soluble in hot water or alcohol, but only difficultly so in cold water.

Allied to bromural in its structure and physiological action is adalin which is a brom-diethyl-acetylcarbamide. The latter is an odorless crystalline powder, freely soluble in alcohol, but only sparingly dissolved by water.

The dose of either of these is from 5 to 15 grains (0.3 to 1 Gm.).

Physiological Action.—The manifest purpose of each of these preparations was to combine the sedative effect of the bromides with the narcotic action of the aliphatic series. It is evident that the action of the bromine ion can only be elicited if the molecule is decomposed in the body. If such a liberation were to take place one would hardly expect any bromine action from the doses which are ordinarily employed, for bromural contains approximately 36 per cent. of bromine, so that the sedative dose of five grains would represent less than two grains of bromine. Takeda finds that by far the larger proportion of bromine in a given dose of bromural appears in the urine in an inorganic —that is, ionic—form and Impens obtained like results with adalin. Takeda believes, however, that the action upon the brain is due to the whole molecule.

Therapeutic Uses.—Bromural is used in medicine for two distinct purposes, namely, to quiet nervous unrest, and to produce sleep. As a somnifacient, it is inferior in power to most of the commonly used

sleep-producing drugs, but may be of service in the milder types of insomnia. On the other hand, it is one of the most serviceable remedies that we possess for quieting general nervousness, hysteria, and similar disturbances. It differs from most of the other narcotics of this series in that it possesses a distinct analgesic effect. The author has found it also of service in the treatment of asthma, and it has been highly recommended as a remedy against sea-sickness.

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ANÆSTHETICS.

All of the aliphatic narcotics, when given in sufficient doses, abolish pain perception. To achieve this result, however, requires enormous doses, far in excess of that necessary to produce sleep. In the condition of complete insensibility known as general anæsthesia it is possible to bring the patient to the brink of death and keep him there for an almost indefinite period of time because of the extreme rapidity with which the substances used for this purpose escape from the system. Surgical anæsthesia is but the extreme degree of hypnosis produced by agents whose volatility prevents their being long retained in the body.

ETHER.

Ethyl oxide [$(C_2H_5)_2O$] is a colorless, volatile liquid, obtained by the dehydration of alcohol by sulphuric acid. It is very inflammable, as is also its vapor, which is two and a half times heavier than air.

It is soluble in about 12 volumes of water, miscible in all proportions with alcohol, and is itself a solvent for many substances, especially the fats. Its odor is strong and characteristic, its taste pungent. When pure it has a specific gravity of 0.713 and a boiling point of about 95° F. The ether of the U. S. Pharmacopœia contains between 96 and 97 per cent. of absolute ethyl oxide. It should be stored in light-proof containers, as exposure to light causes chemical changes which may result in the production of various irritant substances.

Although it had been known chemically for many years and had even been employed by inhalation in the treatment of pulmonary affections, as well as an intoxicant, the first use of it as a surgical anæsthetic was by Dr. C. W. Long, in 1842. Dr. Long, however, did not make known his experiences to the medical world until several years later, and the credit of introducing it as a general anæsthetic belongs to W. T. G. Morton, a Boston dentist, who employed it in his practice in 1846, and later called it to the attention of Dr. Warren, who performed the first surgical operation under artificial anæsthesia in the same year.

Official Preparations:

Ætherum ..... 15 to 60 minims (1–4 mils).
Spiritus Ætheris (32 per cent.) ..... ½ to 2 fluidrachms (2–8 mils).

Physiological Action.—The dominant effect of ether is upon the central nervous system, which is depressed in reverse order to its development; that is, the earliest affected is the brain, next the spinal cord, and finally the medulla. When locally applied it also has a depressant action upon the motor nerves, but this does not occur in the living animal. In the early stages of ether poisoning there is a condition of mental incoherency similar to that produced by alcohol. Later there is complete abolition of the cerebral function. Histological changes have been found in the brain cells, as the result of etherization, consisting of a simplification of the dendritic processes of the pyramidal cells.

Although the earliest effect of ether is usually a disturbance of intellection, the sense of pain is diminished before there is complete loss of consciousness. Whether or not this early loss of sensation is due to an action upon the pain-perceiving parts of the brain, or whether to an influence upon the sensory tracts of the spinal cord, is at present uncertain. The fact, however, which I have experimentally proved, that in the lower animal there is a lowering of the threshold for pain perception at a time while the tendon reflexes still remain and the animal is able to walk, would seem to indicate that the effect is chiefly cerebral. Later there is certainly paralysis of the spinal cord, which Flourens has demonstrated first involves the posterior or sensory ganglia and much later the motor cells. It is frequently possible to produce in the man an

almost complete anæsthesia with the retention of a considerable degree of voluntary motor power.

The peculiar safety of ether, and indeed of all the anæsthetics—for, as remarked above, the condition of anæsthesia is really one of serious poisoning—lies not only in its volatility, which permits its rapid escape from the system in times of danger, but also in the fact that the vital centers in the medulla are involved very late in the poisoning. Event-

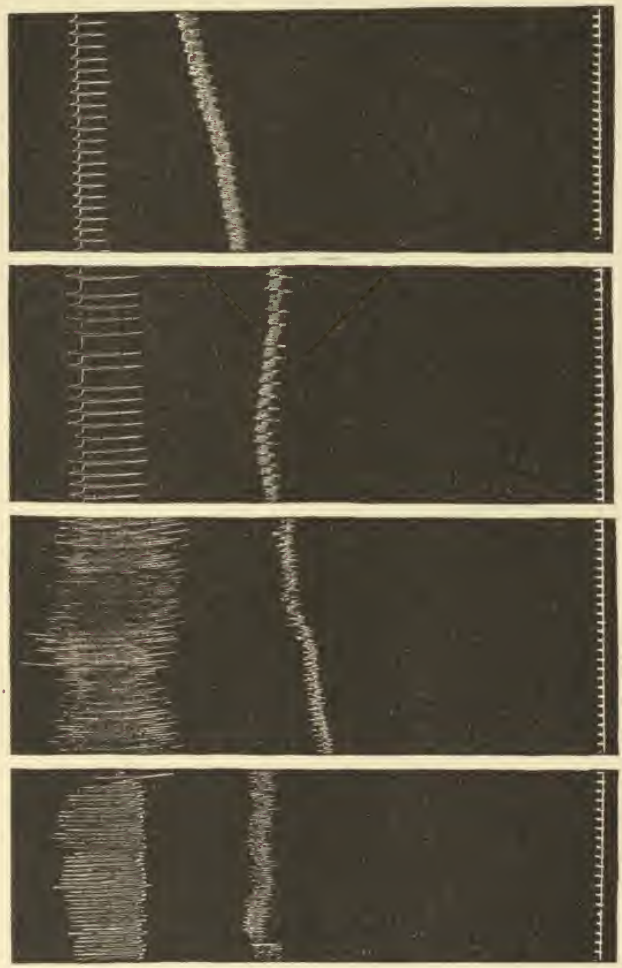

FIG. 9.—Showing the effect of ether on the circulation and respiration. A, Normal. B, Stage of excitement. C, Stage of anæsthesia. D, Beginning of toxic action. Note that the blood-pressure is high despite the dangerous depression of respiration. Time marker indicates 2 seconds.

ually these are affected. The first of them to feel the influence is the respiratory center, and generally in even surgical anæsthesias there is some slowing of respiration. Later in narcosis there is also depression of the vasomotor center and consequent fall of blood-pressure.

Circulation.—The action of ether upon the circulation is comparatively feeble, its injection into the blood stream in the lower

animals producing varying results. Sometimes there is a slight rise and at others a slight fall in the pressure. The probabilities are that the effects of small doses of ether are the same as those of small quantities of alcohol; namely, a slight stimulant action upon the heart, with a widening of the peripheral blood-vessels. Blauel has found that in human anæsthesias under ether there was an increased blood-pressure in 79 per cent. of the cases, lower blood-pressure in 12 per cent., and unaffected in 9 per cent. Just as with alcohol, large doses both weaken the heart and widen the arteries. The statement which is often made that ether acts upon the circulation like chloroform, except more feebly, is in my opinion incorrect; chloroform is from the beginning a depressant, while ether is only eventually so, being a primary stimulant.

Absorption and Elimination.—Ether is rapidly absorbed through all mucous membranes, and, while for surgical purposes it is ordinarily given by inhalation, it must be remembered that it may produce all its characteristic effects when exhibited by the mouth. It is eliminated chiefly through the lungs, although it is possible that small amounts may also escape through the kidney.

Therapeutics.—(For a discussion of the use of ether as an anæsthetic see under Practical Anæsthesia, page 112.)

Ether has been used internally as a carminative in cases of colic. For this purpose the compound spirit has generally been preferred, but is probably not superior to the simple spirit. The drug has also been used as a cardiac stimulant in the treatment of syncope and shock, usually given hypodermically. Its value, however, is doubtful. Locally ether is strongly irritant and, being poisonous to all protoplasm, has some antiseptic action, but is rarely used practically.

CHLOROFORM.

Materia Medica.—Chloroform, which was discovered in 1831 by Samuel Guthrie, of Sacketts Harbor, New York, has the formula $CHCl_3$ and is generally regarded as a trichlormethane. It is produced by the action of chlorine upon alcohol. It is a colorless, limpid, and neutral fluid, with a specific gravity of 1.476. Although practically non-inflammable, it can be made to burn with a greenish flame. Its taste is hot and sweetish, its odor fragrant and peculiar. It is soluble in alcohol and in ether, but almost insoluble in water. The United States Pharmacopœia requires that chloroform should contain, by weight, 99 to 99.4 per cent. of absolute chloroform and 0.6 to 1 per cent. of alcohol. It was first used as an anæsthetic by Sir James Y. Simpson in 1847.

Official Preparations:

Chloroformum ..... 15 to 30 minims (1–2 mils).
Spiritus Chloroformi (6 per cent.) ..... 1 to 2 fluidrachms (4–8 mils).
Aqua Chloroformi (Saturated Solution, about ½ per cent.) ..... 4 fluidrachms (15 mils).
Linimentum Chloroformi (30 per cent.) ..... External use only.

Physiological Action.—*Nervous System.*—The effects of chloroform on the nervous system are precisely the same as those of ether, with the exception that it is much more powerful.

Circulation.—When injected into a vein, or concentrated vapors are inhaled, chloroform causes an immediate fall of blood-pressure, with marked slowing of the pulse. Dogiel pointed out that these phenomena did not occur after previous section of the vagi, and attributed them to stimulation of the inhibitory center, but Embley found that inhalations of chloroform of sufficient strength so reduce the irritability of the motor ganglia of the heart that vagal stimuli which ordinarily would have but very slight influence upon the pulse-rate may cause a marked slowing or even fatal inhibition of the heart.

The changes in the circulation which are caused by dilute vapors of chloroform, as ordinarily administered for surgical anæsthesia, are somewhat different. There is first a slight transient rise in the pressure —a vasomotor reflex from the irritation of the mucous membrane of the upper respiratory tract—followed, generally within half a minute, by a slight lowering of the arterial pressure. Guy, Goodall and Reid find that in human beings the pressure has generally fallen about ten per cent. at the end of the second minute. The pressure tends to fall throughout the whole stage of chloroform anæsthesia, and the lowness of the pressure will be proportionate to the length of the anæsthesia, as well as to the amount of chloroform employed. The fall of blood-pressure produced by chloroform is caused by a direct depressant action upon the heart muscle. Moderate quantities lessen both the tone of the heart and the force of systole. Under increasing quantities the cardiac contraction becomes weaker and weaker until, if the dose be sufficient, the heart is finally arrested in diastole.

The fall of blood-pressure in the early stages of the anæsthesia is purely of cardiac origin—indeed, there is considerable evidence that small quantities of chloroform stimulate rather than depress the vasomotor mechanism—later, however, when the stage of collapse begins, the vasomotor mechanism becomes completely paralyzed. It is because of this vasomotor paresis that elevating the feet of the patient sometimes has such a remarkable influence on the circulation.

It is to be remembered, however, that although the effects of chloroform on the circulation in sufficient doses are pronounced they are secondary to the action upon the nervous system.

Respiration.—In the early stages of chloroform anæsthesia the respirations are usually irregular, as in the beginning of ether anæsthesia, and there may be, as the result of the struggling, a marked increase in the respiratory activity, but as soon as the first stage is over the respirations become reduced in frequency, although the depth is fairly well maintained. If larger doses of the anæsthetic are given the respiration becomes progressively weaker, precisely as in the case of ether. It is probable that the reduction of the blood-

pressure by lessening the nutritive supply to the respiratory center increases the danger of failure of breathing.

General Nutrition.—That chloroform affects the general nutrition of the body is demonstrated by the wide-spread fatty degeneration which sometimes follows long-continued narcosis produced by it. Tedeschi has shown that the first anatomical alteration produced by chloroform is a cloudy swelling of the parenchyma, which may go on to degeneration or may subside; even when a considerable degree of apparent fatty degeneration has occurred recovery is possible. A number of authors have found similar changes in human beings who have died following chloroform anæsthesia.

Müller has observed protoplasmic degenerations not only after chloroform, but also after ether, ethyl chloride, and even chloral hydrate, but none of them so well marked as after chloroform. In his experiments it was found that when a second narcosis was produced before the reparative processes were complete the baneful effects were much intensified, even if different anæsthetics were used. He warns that after prolonged anæsthesia no second narcosis should be undertaken for at least three days.

In this connection may be mentioned also the observations of Becker, who found pronounced acetonuria following anæsthesia. Fatal cases of acetonuria have been reported following ether in children suffering with muscular atrophies.

ETHYL CHLORIDE.

Ethyl chloride is made by heating together a mixture of ethyl alcohol, sodium chloride, and sulphuric acid. It is a colorless, extremely volatile liquid of a specific gravity of 0.918, boiling at 12.5° C. (54.5° F.), and with a characteristic odor suggesting that of ether.

This substance was originally introduced as a means of producing local anæsthesia by freezing. On account of its extraordinary volatility it evaporates so rapidly from the skin as to produce a temperature below the freezing point. It has, however, come to be used to a considerable extent as a general anæsthetic in the same class of cases for which nitrous oxide is suitable, which agent it rivals in the rapidity of its effects.

Ethyl chloride is an example of the fact quoted above that the introduction of a chlorine atom into the molecule of a member of the open-chain series increases both its narcotic power and also its depressant influence. It acts upon the circulation much like chloroform, producing a marked fall in the general blood-pressure.

Clinical experience has confirmed the conclusion of the pharmacologists that this substance is more nearly allied to chloroform than ether. While the statistics, collected by the author, show a mortality after ethyl chloride of only one death in 5,710 administrations, it must be remembered that in the great majority of these cases the anæsthesia was of only a few minutes' duration. Because of the rapidity of its

action it comes in competition with nitrous oxide rather than with the liquid anæsthetics, and it is at least 200 times as dangerous as the gas.

Bromoform is a colorless liquid resembling chloroform in its physical properties, but less volatile.

It was at one time suggested as a general anæsthetic, but it has no advantage over chloroform and is more dangerous. Its only use at present is as a sedative in the treatment of whooping-cough. For this purpose three to five drops may be administered several times a day. To children the dose should be proportionately smaller.

Ethyl Bromide is a colorless, very volatile, mobile liquid, having the specific gravity 1.49, of a sweet, chloroform-like smell; not readily inflammable. Any preparation of it which has color, or seems irritating, or has a disagreeable smell, is unfit for medicinal use. Ethyl bromide degenerates under the influence of light and air, and should, therefore, always be kept in small bottles of dark glass, closely corked.

The effects of this substance upon the circulation seem to be similar to those of chloroform. It is asserted that it differs from the other anæsthetics in that it does not produce muscular relaxation. The drug has no advantage sufficient to warrant its use.

Pental.—Trimethyethylene has been used as an anæsthetic under the name of pental. It is a colorless, highly inflammable liquid, boiling at 100° F. It acts very promptly and is less disagreeable than most of the other anæsthetics. According to the statistics of Curlt, however, it has given a mortality of one death in two hundred narcoses.

NITROUS OXIDE.

Materia Medica.—Nitrogen monoxide is a colorless, almost odorless gas, of a sweetish taste. It is an active supporter of combustion. It is made by the distillation of ammonium nitrate, which resolves itself into the gas and water, and is now supplied in condensed form.

Nitrous oxide was discovered chemically in 1776 by Priestly, but, although it was suggested as a means of producing anæsthesia by Humphry Davy in 1800, it was not until 1844 that the first practical application was made of it by Horace Wells, of Connecticut.

Physiological Action.—Although several observers have shown that in the anæsthesia of nitrous oxide there is a great lack of oxygen in the blood, and although it has been shown that it is possible to produce in the mammal a similar condition by the inhalation of pure nitrogen, it can no longer be doubted that nitrous oxide has a specific action upon the brain. Goldstein has shown that frogs retain their consciousness in an atmosphere of nitrogen, but are anæsthetized by pure nitrous oxide. Paul Bert found that by exposing a dog in a chamber, in which the air was compressed until the pressure was two atmospheres, a mixture of nitrous oxide and 15 per cent. of oxygen

produced anæsthesia. In 1891 Van Arsdale succeeded in producing anæsthesia in the human being with a mixture of oxygen and nitrous oxide in the same proportions as employed by Paul Bert, without prominent symptoms of asphyxia. As ordinarily administered, however, there is always marked asphyxia, which probably plays a greater or lesser part in the anæsthesia.

Outside of its effect upon the brain the gas seems to have almost no effect upon the system.

Therapeutics.—Nitrous oxide is certainly the safest of all the anæsthetics. Although freely administered by persons without medical knowledge, and under all sorts of conditions, the mortality from nitrous oxide is not more than one in a hundred thousand anæsthesias. If pushed to the fatal limit in the lower animals death results always from asphyxia. Even when alarming symptoms occur during nitrous oxide anæsthesia, the results are rarely disastrous, because the loss of function has been due, not to the presence of a poison, but to the absence of oxygen, and, although the paralysis may be complete, the life-power sleeps before it dies, and is ready to react to oxygen. Immediate artificial respiration is the one remedy for the treatment of alarming symptoms during nitrous oxide asphyxia.

Diabetes has been said to occur as the result of anæsthesia with nitrous oxide, but it is improbable that it can produce such effect. On account of the high blood-pressure caused by the asphyxia which occurs during nitrous oxide anæsthesia atheroma or other diseases of the arterial walls should be considered a contra-indication to the use of the gas; fatal apoplexy has occurred from its administration.

Administration.—The difficulty with the practical use of nitrous oxide for other than the brief anæsthesia, such as is required in teeth extraction and other forms of minor surgery, has been the extreme fugaciousness of its action.

Nitrous oxide is often used in conjunction with ether, the primary anæsthesia of nitrous oxide allowing the patient to pass under the ether without the unpleasant excitement. This method is probably safer than ether alone, because of the smaller amount of ether required.

PRACTICAL ANÆSTHESIA.

Choice of Anæsthetics.—For short operations, those which do not last more than four or five minutes, nitrous oxide should almost always be the anæsthetic of choice, not only because it is the least unpleasant for the patient and much quicker in its effects, but especially because of its extraordinary safety. In persons with marked arterial sclerosis, because nitrous oxide produces so great an elevation of the blood-pressure, preference is usually given to one of the liquid anæsthetics. The greatest drawback to nitrous oxide is its bulkiness and consequent difficulty of transportation.

Recently a number of prominent surgeons have vigorously advocated the use of nitrous oxide for major operations. It is indisputable that a skilful anæsthetist can maintain a condition of satisfactory anæsthesia for indefinite lengths of time by a combination of nitrous oxide with oxygen. It is extremely questionable, however, whether it is superior to the liquid anæsthetics in major surgery. In the first place, it is difficult to produce complete relaxation of the patient, and, moreover, it requires a considerable degree of experience and skill in its use to prolong even a condition of partial unconsciousness without danger. It is, moreover, by no means certain that if widely used as a general anæsthetic in major surgery it would show a much lower mortality than ether.

In the opinion of the author neither nitrous oxide nor any of the numerous volatile liquids which have been suggested for anæsthetics are so routinely reliable as ether or chloroform for major surgery. The question as to which of them should be preferred is a vital one, as are also the questions how to recognize and how to treat the accidents which occur during anæsthesia. It must be, in the beginning, granted that the production of anæsthesia is always attended by a danger which, though small, is positive, and that fatal accidents will always occur from time to time. There are few things in medical literature more tiresome than the arrogant assertions of various surgeons that they have never had a fatal accident from chloroform or ether because of the special methods by which they have used them. May their conceit die with them! All that a surgeon can hope for is to reduce the number of these accidents to a minimum.

Chloroform has the advantages over ether—that it produces anæsthesia much more quickly, that it is less unpleasant to the patient, usually does not cause so much struggling, and is less likely to be followed by after-nausea and vomiting. These advantages, while not to be lightly thrust aside, are not to be compared in importance with the question of the comparative danger of the two anæsthetics. We may reach a conclusion as to this factor either by studying the statistics of actual anæsthesia on man, or by a comparison of the physiological action of the two drugs.

The study of the physiological effects of the drug must lead the unprejudiced to the conviction that chloroform is much more dangerous than ether. Chloroform is, at least, as active a respiratory poison as ether, and, besides, is a direct depressant to the heart, while the effects of ether upon that organ are comparatively slight; but, while chloroform is certainly much more depressant to the heart than ether, the danger is not merely in its injurious action upon the heart, but in its peculiar treachery. There have been reported a number of cases of sudden heart-failure from chloroform occurring even before the patient had absorbed enough of the remedy to produce unconsciousness. These deaths have

been attributed to the sudden inhalations of large quantities of chloroform, and by Embley to irritation of the vagus, he having found that chloroform greatly increases its sensitiveness towards inhibitory stimuli. Levy believes that small quantities of chloroform predispose the heart muscle to fibrillation. Another important danger of chloroform is that of the so-called delayed poisoning. There is such a mass of evidence to-day that death from protoplasmic degenerations may occur several days after anæsthesia that even the most sceptical must acknowledge the reality of this peril. Although it is probable that similar changes may be caused by the prolonged inhalation of ether, they are certainly much more frequent after chloroform.

The conclusions of the physiologists that chloroform is more dangerous than ether have been abundantly confirmed by clinical experience. Although it is doubtful whether one-half of the deaths caused by anæsthetics are reported—and statistics of fatalities as a means of determining the danger of anæsthesia are, therefore, unreliable—yet when we come to compare the danger of two anæsthetics, the error being as great in one case as in the other, the statistical information is entirely trustworthy. Especially is their value assured in view of the tremendous number of cases covered—amounting to several millions of anæsthesias—and the close agreement between most of the various authors who have investigated this problem. These statistics show an average mortality for chloroform of about one death in 3,500 anæsthesias, and for ether about one in 15,000. Taking into consideration the evidence of the laboratory worker and of the statistician, the conclusion is inevitable that under ordinary circumstances chloroform is about four times as dangerous as ether.

There are certain diseases, however, which may make ether unusually dangerous. Among these the most important are various pulmonary affections. The local irritant action of ether vapors upon the mucous membrane of the respiratory tract may cause a serious exaggeration of a comparatively trivial pulmonary infection, and, except in cases in which the heart has been weakened, as in chronic emphysema, chloroform should generally be given the preference over ether in pulmonary complaints.

There is a common belief among surgeons that ether is more irritant to the kidneys than chloroform, a belief which appears to be founded upon the fact that post-anæsthetic nephritis was first demonstrated after ether, but the most recent studies of this subject show that chloroform is at least equally irritant, and probably more so, to the renal structure than is ether. This might naturally be expected when it is remembered that the chloroform is eliminated chiefly through these organs. In those not uncommon cases of advanced nephritis where there is involvement of the heart the depressant action of chloroform on this organ would exclude it from consideration. On the other hand, when the nephritic shows a tendency to dropsical effusions it is probable that the irritation of the mucous membrane

of the lungs by ether increases the danger of pulmonary œdema. The author's belief, therefore, is that ordinarily in Bright's disease ether should be given the preference, but that when dropsy exists chloroform is the less dangerous.

There are certain other conditions that will lead to the preference of chloroform. Thus, the inflammability of ether vapors almost prohibits the use of this agent when it is necessary to operate in the neighborhood of a naked flame; also the greater power, in proportion to its bulk, of chloroform makes it easier of transportation, and in military expeditions it is often the only anæsthetic possible to obtain.

Examination of the Patient.—Before administering the anæsthetic, careful examination should be made by the anæsthetizer for the determination of any physical condition which would enhance the danger of the anæsthesia. Among these conditions most commonly to be looked for are: organic brain diseases, including tumors; atheromatous conditions of the blood-vessels; organic affections of the heart, of the lungs, and of the kidneys.

Brain.—Brain tumors and other organic forms of cerebral disease are very serious contra-indications to the use of anæsthetics; even where there is no demonstrable brain-lesion if there be reason strongly to suspect atheroma of the cerebral vessels anæsthesia should be induced with the greatest reluctance. In a number of cases apoplexy has resulted during or immediately after the anæsthesia. Moreover, death has frequently abruptly occurred immediately after the sudden removal of a large cerebral tumor, the introduction of the finger between the lobes of the brain, or other procedure which affects the intracranial pressure. These deaths have resulted both from respiratory failure and from sudden cardiac arrest, and are probably the result of the loss of the resisting power of the respiratory and vasomotor centers, making them unable to withstand variations of brain-pressure which in their normal condition would not seriously influence them. It is evident that the surgeon should be as careful as possible in his operative procedures to avoid sudden disturbances of the brain. Which anæsthetic is to be given the choice, in diseases of the brain, there is not yet sufficient evidence to clearly indicate.

Heart.—When valvular disease of the heart does not produce any distinct functional disarrangement of that organ, and when the heart muscle is in a fair condition of health, anæsthesia may be induced, provided the circumstances of the case are such as to justify the surgeon taking a slightly increased risk. The key to the situation is not the valvular lesion, but the condition of the muscle. A loud murmur usually depends for its loudness not only upon the character of the valvular lesion, but also upon the force which drives the blood through the diseased orifice. A loud murmur is, therefore, on the whole, not more strongly contra-indicative of anæsthesia than is a feeble one; indeed, as the feeble murmur is more commonly associated with feeble heart walls, greater care must be exercised when

such murmur exists than when there is a loud one. In cases of heart-disease, if it be possible to avoid the use of an anæsthetic by the employment of local anæsthesia, this should be done. When operation is imperative and local anæsthesia for any reason impossible, the surgeon is justified, even in the presence of serious disease of the heart, in employing a general anæsthetic. The pain and shock of a major operation may throw a greater strain upon the heart than ether, carefully administered.

In diseases of the heart the action of chloroform upon the heart makes it very dangerous. The belief that nitrous oxide is innocuous in cases of heart disease is far from the truth. The high blood-pressure which occurs during nitrous oxide anæsthesia may be sufficient to entirely overcome the reserve power of a diseased heart and lead to serious rupture as compensation.

Lungs.—Organic disease of the lungs seems to be a less serious bar to the use of anæsthetics than might naturally be expected. The danger appears to be in proportion to the acuteness of the disease rather than to its extent. A chronic pulmonary condition, such as tuberculosis, may involve a considerable proportion of the pulmonary area without forbidding the use of the anæsthetic, while in ordinary acute bronchitis the anæsthesia may be attended with grave risk. Only under the most urgent circumstances should anæsthesia be attempted when in an acute pulmonary disease the symptoms are of sufficient intensity to produce even slight dyspnœa.

Of the chronic pulmonic affections probably emphysema associated, as it so frequently is, with weakness of the right heart causes the most solicitude to the anæsthetizer. The irritant local action of ether is an important element when the lining membrane of the tubes or air-vessels is seriously implicated; indeed, my own opinion is very positive that in some of the deaths which have occurred in persons with diseased kidneys from œdema of the lungs directly after etherization the cause of death has been the local irritant action of the ether. The dictum of Hewitt, that in extreme emphysema, in chronic bronchitis attended by expectoration and dyspnœa, and in advanced pulmonary phthisis, chloroform or some other mixture containing chloroform should be employed, is, I believe, correct.

Hepatic Conditions.—L. G. Guthrie has called attention to the excessive fatality attending the use of chloroform in children suffering from fatty degeneration of the liver. The time of death in nine recorded cases was from ten hours to nine days after the operation, so that the cases really belong among those considered in the after-effects of an anæsthesia (see page 109). There is sufficient ground for the generalization that anæsthesia should be produced with the greatest reluctance in all persons suffering from chronic fatty degeneration of the liver, and that when anæsthesia must be produced in such cases ether and not chloroform should always be selected.

Diseases of the Kidney.—So far as our reading goes, Thomas A. Emmet was the first to report cases of fatal urinary suppression

produced by the inhalation of ether in persons suffering from chronic Bright's disease. His statements have been followed by reports of numerous similar cases, and led to the wide-spread opinion that ether should not be used when there was chronic disease of the kidneys. It is now, however, established that chloroform is capable of causing severe renal irritation, and the whole drift of the evidence is to show that in this respect it is much more active than is ether, so that, though renal disease is a contra-indication to the use of any anæsthetic, if anæsthesia must be produced under the circumstances, ether is safer than is chloroform.

In regard to the preparation of the patient, aside from his physical examination, the rules are very simple, but very important.

It is usually recommended that except in emergencies anæsthesia should not be produced in less than six hours after a meal, but Chalfant believes that carbohydrate starvation predisposes to acidæmia. The clothing should be loose, so as to not obstruct in any way respiratory movements; false teeth and other movable objects should be taken out of the mouth. The patient should always be in a recumbent position.

Symptoms.—The narcosis produced by ether and chloroform may be, for convenience, divided into three stages: First, excitement; second, anæsthesia; third, collapse.

The first stage is usually more marked with ether than with chloroform. The first symptoms observed are a sense of choking, which is referable to the irritant action of the vapor upon the mucous membranes of the upper respiratory tract. This irritation of the fauces may lead to great irregularity or even to complete cessation of the respiration. Partly as a result of the irritation of the respiratory tract, but largely on account of the alcohol-like delirium produced, the patient struggles more or less violently. As in alcohol, the delirium of ether or chloroform is of various characters; some patients weep, others laugh, some pray, some rave, and some become pugnacious. In this stage the patient in most cases may be more or less perfectly aroused, although there is marked diminution or complete loss of pain perception. In rare instances consciousness has been retained until complete anæsthesia. The face is warm, flushed, and moist. The pulse is somewhat more rapid than normal, largely on account of the struggling of the patient, but of good volume. The pupil may be somewhat dilated, but readily contracts to light.

The second stage is that of surgical anæsthesia. There is complete loss of sensation with unconsciousness, the patient being in a deep stupor from which he cannot be aroused. The reflexes are mostly abolished, although certain ones, as the conjunctival and respiratory reflexes, may be retained. The muscles are relaxed, but keep their tone.

The third stage is one of collapse and danger. The relaxation becomes more complete and there is also often loss of muscular tone, which gives rise to some of the danger signals, such as stertorous

respiration and changes in the expression of the face. The pulse is rapid and feeble, the respirations are shallow and far apart, the skin is either livid or pale, or often of a peculiar cyanotic pallor, the pupils are widely dilated. All the reflexes, including the so-called vital reflexes, are also lost. Death, if it occur, may be due either to respiratory- or heart-failure, the former being the more frequent termination with ether, the latter with chloroform.

Administration.—The methods of producing anæsthesia with chloroform and ether differ to a certain extent and must be considered separately. In administering ether the so-called "closed inhalers"—that is, those in which the patient breathes in and out of a closed receptacle—should always be avoided. One of the best forms of inhalers is that invented by Dr. O. H. Allis, of Philadelphia. Equally good results may be obtained, however, with a three- or four-layer of gauze laid over the face.

The inhaler invented by O. H. Allis is based upon the theory that the patient to be etherized should be supplied with an abundance of air impregnated with the vapor of ether. It consists essentially of a series of foldings of muslin on a wire framework, arranged almost like the gills of a fish, so as to allow the air to pass freely through, but everywhere to come in contact with the ether.

In the beginning of the anæsthesia but one or two drops of ether should be placed upon the inhaler at a time (with nervous patients it is often advisable to place the inhaler over the face for a minute or two without any ether at all); ether is then added slowly drop by drop, at the slightest sensation of choking removing the inhaler and allowing the patient to take three or four breaths. If the ether is increased gradually in this manner it is usually possible to bring the patient to unconsciousness with little discomfort. As soon, however, as the patient commences to struggle and show symptoms of delirium the ether should be used very freely, so that the inspired air is as nearly as possible saturated with the narcotic vapors, until the patient becomes completely anæsthetized. After the second step is reached only small quantities of the anæsthetic are required to keep the patient unconscious.

With chloroform it should be the invariable rule that the vapors be in as dilute form as possible to produce anæsthesia. A single whiff of concentrated vapor of chloroform has proven fatal. The inhaler generally preferred for chloroform is the Esmarch inhaler. It consists of a piece of stout wire bent to fit over the mouth and covered with a single layer of gauze. Many anæsthetists use a piece of gauze held over the mouth and nose. If this latter method is used the gauze should never be allowed to come in contact with the face; whatever apparatus is employed, it is essential to allow an air space between the face and inhaler so that the chloroform vapors shall not be inhaled undiluted.

During the anæsthesia the unconsciousness of the patient can

usually be judged by the preservation or absence of the corneal reflex. With ether, and to a certain extent also with chloroform, the degree of the contraction of the pupil offers a handy, but unreliable, criterion of the depth of the narcosis and the approach of the third stage. The pupils should ordinarily be kept in a condition of medium contraction. This sign, however, is not to be relied upon, as some patients show great idiosyncrasies. The rate of the respirations, the rate of the pulse, the color of the skin, and the expression of the face should all of them be watched for signals of danger. It is evident that the anæsthetist has all that he can possibly attend to if he is properly watching the administration of the anæsthetic, and he should, therefore, never be expected nor allowed to take an interest in the operation outside of his immediate duties.

Accidents.—The danger signals, or signs of threatening collapse, are as follows: sudden dilatation of the pupils, very slow or very shallow respiration, sudden increase in the pulse-rate or great diminution in the volume of the pulse, stertorous breathing (the result of the loss of tone in the muscles of the soft palate), changes in the color of the skin—either lividity or pallor—and changes in the expression of the face—such as drooping of the corners of the mouth (loss of muscle tone in the facial muscles).

At the appearance of any one of the danger signals described above the anæsthetic should be immediately withdrawn.

In the light of all our present clinical and experimental knowledge, the following rules may be formulated as embodying the treatment of accidents of anæsthesia:

1. Unless the pulse be beating actively, partially or wholly invert the body of the patient.

2. Place the index-finger of each hand upon the corresponding cornua of the hyoid bone, whilst the middle fingers rest upon the angle of the jaw, and then press forward and upward, the same force serving to extend the head upon the neck; if this fail to open the glottis, draw forward the tongue by means of a tenaculum or hæmostat.

3. Make a momentary effort to stimulate respiration by slapping the chest, by douching with cold water, or by the method, suggested by Hare, of pouring a little ether on the bared abdomen, so as to get the effect of cold. Do not waste time, if respiration has failed, in any of these attempts.

4. Use certain drugs as follows: Ammonia, hypodermically, may sometimes be of value to stimulate the heart. Strychnine and cocaine, administered hypodermically or intravenously, are probably the most generally useful drugs. Digitalis given hypodermically acts too slowly to be available; strophanthin injected intravenously might be a very valuable remedy, but we know of no clinical records of such use. Adrenalin, especially in cases of cardiac failure, administered intravenously in hot (105° F.) normal saline solution, may be of service;

from twenty to thirty minims of the 1 to 1000 adrenalin solution in half a pint of the saline solution may be slowly injected in cases of persistent circulatory failure; as much as two drachms of the adrenalin solution in two pints of the normal saline may be given in the course of one and a half hours. When the symptoms are not very alarming, smaller amounts than those spoken of above are preferable.

5. Practise artificial respiration immediately and very actively throughout (forced respiration if the apparatus be at hand), even when the heart is primarily affected. It must be remembered that the residual air of the lung may retain the vapor of the anæsthetic and continue to yield it to the system for a considerable time after the cessation of its administration.

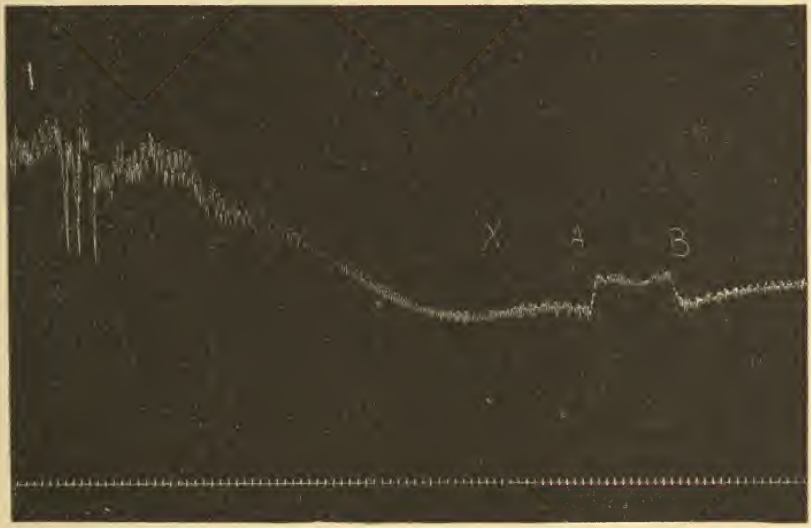

FIG. 10.—Showing the effect of elevating the feet during chloroform narcosis. I, Begin chloroform inhalation. X, Withdraw chloroform. A to B, Feet raised above head. Time marker indicates 2 seconds.

The one measure which surpasses in practical efficiency all others combined is artificial respiration, by means of which animals have frequently been resuscitated after all cardiac and respiratory movements had apparently ceased.

It is evident that the ordinary methods of practising artificial respiration in man are exceedingly imperfect and feeble, and that in the accidents of anæsthesia so-called forced artificial respiration should be at once employed. The principle of forced artificial respiration consists simply of pumping air into the lungs by means of a bellows, as with Fell's apparatus. When no apparatus is at hand, forced insufflation by breathing into the patient's mouth may be tried.

6. In many cases much advantage may be obtained by elevating

the feet. The body of the animal whose vasomotor system has been paralyzed by chloroform acts in a measure like a tube filled with liquid. When the feet are raised above the head there is a marked increase in the blood-pressure in the carotid, with decrease in the blood-pressure in the femorals; and when, on the other hand, the feet are dropped below the head the blood-pressure falls in the carotid, but rises in the femorals. The respiration is not affected by the procedure, but a heart which has entirely ceased will often suddenly resume its work when the feet are elevated. Inversion causes the blood which has collected in the extremely relaxed abdominal vessels to flow into and distend the right side of the heart, and this distention may have sufficient influence to stimulate into action a failing organ.

Cardiac Massage.—In the lower animals, after fatal amounts of chloroform, life may frequently be restored by rhythmical compression of the heart, and the so-called cardiac massage has been employed to a considerable extent by surgeons, and several instances of its successful use have been recorded. Three methods have been used: (1) By compression between the hands, one being applied outside the chest and the other directly upon the heart after an abdominal section, but without opening the diaphragm; (2) by abdominal section, and, after opening the diaphragm, seizing the heart within the pericardial sac; (3) by resection of the chest wall, and grasping the heart with one or both hands. The third of these methods involves a major operation in surgery, requiring much time for its performance and adding distinctly to the surgical dangers of the patient. Especially when the abdomen has already been opened by the surgeon, the first, or even the second, method is easily practised without very serious surgical results.

The value of cardiac massage very probably does not reside solely in its effects in forwarding the flow of blood, but also, to a large extent, in the mechanical stimulation of the heart muscles. If this view is correct, some benefit would be derived from a vigorous massage on the chest over the precordial area, and we have several times seen in the dog the arrested heart recommence its activity as the result of this operation. King has reported two cases in which life was apparently saved by sudden rapid compression with the ball of the thumb over the precordial region.

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ANALGESICS.

The methods and agents for relieving pain differ greatly according to the source and character and severity of the suffering. In pains of great intensity but of short duration, such as are typified in surgical conditions, the use of the volatile anæsthetics, although most frequent in surgical procedures, is often serviceable even in other types of pain. In various unpleasant sensations arising from inflammatory conditions of the skin or mucous membrane, or immediately underlying areas, relief can often be obtained by the use of local anæsthetics without any perceptible effect upon the general organism. There are, however, a vast number of cases in which neither of these groups of agents, nor yet the various non-medicinal measures, are sufficient, and we have recourse to those drugs which depress the pain-perceiving centers of the

brain. How these drugs produce their beneficent effect is entirely unknown. Since, except in one or two instances, they do not diminish the reflex activity, it is evident that they act upon some portion of the nervous system higher than the spinal cord; presumably they paralyze some centers in the cerebrum.

Another interesting, but little understood, point in the action of these remedies is their synergistic effects. It appears that when two anodynes, belonging to different chemical groups, are used simultaneously in relatively small doses, their effect is very much greater than would be merely the sum of the effects of each; but, on the other hand, where two anodynes of similar chemical groups are used together their effect will be exactly the sum of the two effects of each. Clinicians have long known that combining anodynes of different groups, such as morphine with antipyrine or the bromides, the desired effect can be obtained with relatively small doses.

OPIUM.

Materia Medica.—Opium is the dried juice obtained from the unripe capsule of the *Papaver somniferum,* or white poppy. This plant is a native of Asia and was cultivated as far back as the time of Homer for the sake of its beautiful white flowers. The medicinal properties of the plant have been known for at least 2000 years, and Dioscorides described the method of collecting opium at the beginning of the Christian era, which was practically the same as that employed to-day. The plant is extensively cultivated in India, China, Persia, and Asiatic Turkey. Immense quantities of it are produced, the importations of the United States alone being in the neighborhood of one and one-half million pounds annually.

The *Papaver somniferum* is a herb growing to the height of two to six feet, producing large, showy white flowers of a shape similar to that of our native red poppy. The active ingredient seems to be present in the plant only during fruition. Opium is obtained by incising the capsule (fruit) before it has ripened and allowing the juice to exude for twenty-four hours and then collecting. Several varieties of opium are recognized, according to the country from which they enter commerce, as India opium, Persia opium, etc. Practically all that comes to the United States comes through the port of Smyrna and is known as Turkey or Smyrna opium. It occurs in large, irregular lumps, weighing from a quarter of a pound to two pounds, of a brownish mottled color, frequently with the remnants of poppy or plants adhering to its surface. It has a peculiar odor, described as narcotic, somewhat resembling unroasted coffee, and a bitter taste. It is completely soluble in dilute alcohol, and, although not entirely dissolved, yields its activities to water. It is a very complex body, containing the alkaloids morphine, codeine, narceine, narcotine, thebaine, papaverine, porphyroxine, cryptopine, meconine, opianine, and paramorphine, besides meconic, thebolactic, and sulphuric acids, extractive matter, gum, glucose, fixed oils, a volatile odorous principle,

and other substances of no importance. Of its ingredients, by far the most important is morphine, and the United States Pharmacopœia directs that crude opium shall contain not less than 9.5 per cent. of this alkaloid.

Morphine is obtained by precipitation with ammonia water from an infusion of opium. It is very slightly soluble in water, but, like the other alkaloids, forms soluble salts with various acids. The other alkaloids more or less modify the effects of the morphine; thus Macht has shown that, so far as the respiratory center is concerned, codeine is synergistic and narcotine and thebaine antagonistic to morphine, and that opium is less depressant to respiration than is the morphine it contains.

Incompatibilities.—Opium is incompatible with the alkaloid precipitants, as alkalies, tannic acid, corrosive sublimate, iodides, etc. Besides these, on account of the meconic acid, it precipitates the salts of many metals, notably lead acetate.

Official Preparations:

There are six *solid* preparations of opium official in the United States Pharmacopœia:

Opii Pulvis (12 per cent. Morphine).....½ to 2 grains (0.03–0.12 Gm.)
Opium Deodoratum (12 per cent. Morphine)....½ to 2 grains (0.03–0.12 Gm.).
Opium Granulatum (12 per cent. Morphine)....½ to 2 grains (0.03–0.12 Gm.).
Extractum Opii (20 per cent. Morphine).....½ to 1 grain (0.03–0.06 Gm.).
Pulvis Ipecacuanhæ et Opii [Dover's Powder] (10 per cent. each of ipecac and powdered opium) .....3 to 10 grains (0.2–0.6 Gm.).

The *liquid* preparations each represent ten per cent. powdered opium, except the camphorated tincture. It should be remembered that one minim of tincture of opium is equal to almost two drops.

Tinctura Opii [Laudanum] (10 per cent.).....5 to 15 minims (0.3–1.0 mil).
Tinctura Opii Deodorata (10 per cent.).....5 to 15 minims (0.3–1.0 mil).
Tinctura Opii Camphorata [Paregoric] (Powdered opium, camphor, benzoic acid, oil of anise, each 0.4 per cent.).....1 to 4 fluidrachms (4–15 mils).

The following preparations of morphine are recognized:

Morphina .....⅛ to ¼ grain (0.008–0.015 Gm.).
Morphinæ Hydrochloridum .....⅛ to ¼ grain (0.008–0.015 Gm.).
Morphinæ Sulphas .....⅛ to ¼ grain (0.008–0.015 Gm.).

Physiological Action.—Crude opium is locally irritant, probably because of its resinous matters, for morphine has no such irritant properties. Although Wiki has shown that morphine and some of its derivatives have a feeble local anæsthetic action when injected beneath the skin, this effect is too weak to be of any practical value. The use of these agents, therefore, as local remedies, while common, is not justified by our knowledge of their effects.

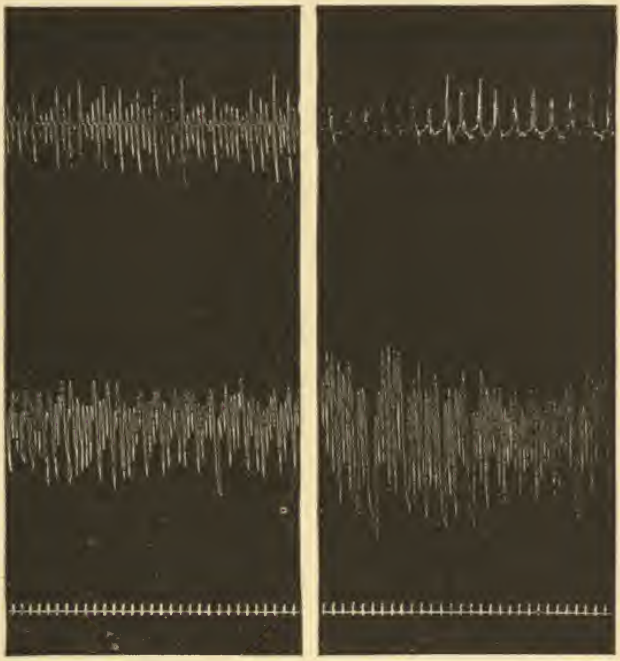
The dominant action of morphine in man is upon the brain. In-

deed, after small doses the only perceptible evidences of its effects are of cerebral origin. It has, however, a distinct effect even in therapeutic doses upon certain medullary centers and a not clearly understood action upon various secretions.

Nervous System.—The symptoms produced by morphine in various animals differ widely. This dissimilarity of symptoms, however, is not due to any difference in the kind of action of the alkaloid, but is solely the result of the different relative development in the brain and spinal cord in various animals. In those animals with a highly-developed cerebrum, such as man, the alkaloid tends to produce sleep, while in those animals whose brain is poorly developed, such as the frog, the stimulant action upon the spinal cord leads to the occurrence of convulsions. Between these two extremes we have all degrees of mixed effects; for instance, in the dog the symptoms are very similar to those produced in man, although there is generally some exaggeration of the reflexes; in the horse there is a primary stage of excitement, followed by sleep, although true convulsions are rare; in the cat the convulsive action generally prevails. In man, during the morphine sleep, not only are the reflexes usually not increased, but they are often diminished. A similar effect is observed in the lower animals, even in those like the frog, in which there is a poorly-developed cerebrum, in so far that the stage of convulsions is preceded by a stage of diminished reflex activity. Various explanations of this lessening of reflexes have been given, but the one that seems to me most harmonious with all the facts is that which is based upon the hypothesis of a spinal inhibitory center. There is considerable physiological evidence that in frogs, at least, and presumably in other animals, there is located in the optic lobes a center, commonly known as Setschenow's center, whose function is to control reflex activity, and stimulation of which diminishes reflexes. It would appear plausible that morphine in small doses excites this center so that the spinal activities would be lessened, but that the large dose stimulates the ganglia in the gray matter of the spinal cord, perhaps also paralyzing the inhibitory center at the same time, thus producing marked increase of reflexes and even convulsions.

Sufficient quantities of morphine in man produce sleep, which, like the sleep produced by the somnifacients of the fatty acid series, in its lighter forms closely resembles natural sleep. There is a marked difference between the effects of morphine and the methane homologues upon the brain, for, whereas the latter destroy the sense of pain only after very large doses—that is, quantities much greater than are required to produce sleep—the effect of morphine upon pain perception is noticeable even with the physiologically minimal dose. While there is after morphine some interference with the receptive cells for nearly all the afferent impulses, so that, for instance, the acuity of the touch sense is diminished, these effects are not so marked as the diminution in the sense of pain.

The effects upon the intellectual activities are similar in kind to those produced by alcohol. There is with certain individuals, especially those who are habituated to the use of the drug, in the early stages of its action, a subjective sense of increased intellectual power and often a real exaltation of the imaginative function, but the true intellectual activities, such as those involved in the various psychological tests and those which are useful in the daily struggle for existence, are diminished from the beginning of its action. In the lighter degrees of the morphine narcosis, as in normal sleep, the patient can be easily



(Before injection.) (After injection.)

FIG. 11.—The effect of opium on circulation and respiration. Note the great slowing of respiration, also the slowing of the pulse without much change in the blood-pressure.

aroused, but when left to himself usually dozes off again. After large doses of the drug, however, it becomes progressively more and more difficult to awaken the subject, until with very large toxic doses there may be produced a condition of complete coma.

Circulation.—The important fact concerning the action of morphine upon the circulation is that it is insignificant. In therapeutic doses, and even after slightly toxic quantities, the blood-pressure remains the same; the only evidence of an action upon the circulation is a dilatation of the vessels of the skin, leading to a flushing of the

surface, especially of the face, and a slowing of the pulse. The slowing of the pulse is due to a stimulant action upon the cardio-inhibitory center in the medulla. During this stage of action there is sometimes, although not always, a slight increase in the blood-pressure, which, considering the fact that the heart is slowed, suggests a slight stimulant influence on the cardiac muscle. After large toxic doses there is an increase in the rate of the pulse due to paralysis of the peripheral ends of the pneumogastric and some fall of the blood-pressure, probably the result of combined depression of the heart and vasomotor system.

Respiration.—The characteristic effect of morphine upon the respiratory center is to lessen its activity, diminishing especially the rate and, in full doses, also the depth of respiration. In fatal cases of

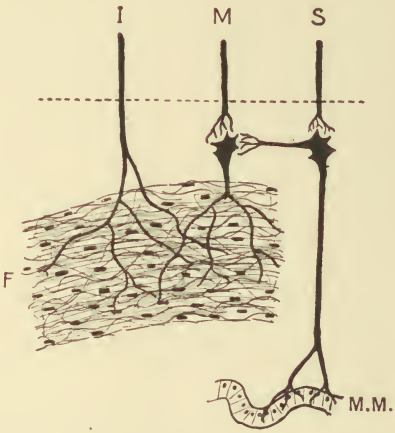


FIG. 12.—Diagram to show how opium influences intestinal movements. M M, Mucous membrane. S, Sensory nerve. M, Motor nerve. I, Inhibitory nerve. F, Muscular fibres. The structures between the dotted line and the muscular layer constitute Auerbach's plexus. Opium appears to check peristalsis by stimulating I.

morphine death is due practically in every instance to respiratory failure. Morphine has, however, an effect upon the respiratory center which is something more than a mere diminution in its functional activity. In some way it lessens what we may speak of as the reflex activities of this center, so that there is a reduction in the susceptibility to those influences which give rise to abnormal respiratory movements, such as coughing, asthma, and the like.

Secretions.—Most of the secretions of the body are lessened by morphine, although the sweat is often increased because of the dilatation of the peripheral blood-vessels. The mechanism of this diminution of secretory activity is as yet unknown, but the experiments of Thompson indicate that at least as far as the kidney is concerned the action is a direct one.

Digestive Tract.—Intestines.—Opium, and to a less extent mor-

phine, has a very pronounced influence upon the digestive tract, in many persons producing nausea, in all lessening the appetite and the activity of digestion and causing constipation. The disorder of digestion and the constipation are in part, at least, due to an arrest of secretion, probably both in the stomach and in the intestines; but they are also probably to some extent due to the checking of peristalsis, an effect which can often be shown in men, and which Nothnagel and Ott have demonstrated upon animals. According to Magnus, the effect on peristalsis occurs after dividing all of the nerve-trunks passing from the sympathetic system to the intestines. He believes the action is upon the plexus of Auerbach. In the dog morphine often leads to the expulsion of feces. It must be noted, however, that we can hardly compare the effects produced in dogs to those of man, because of the difference in doses. There is reason to believe that in corresponding doses opium produces in dogs, as in man, a diminution rather than an increase in the intestinal peristalsis.

The effects of opium upon the intestines are much more marked than those of morphine. To which element of the opium this is due is uncertain. Vamossy investigated a large number of the opium alkaloids and found that none of those he studied was equal to the opium in their constipating effects.

Eye.—In full doses morphine produces a contraction of the pupil the degree of which is in proportion to the largeness of the dose. It is frequently stated in text-books that in the last stages of opium poisoning there is a paralytic dilatation of the pupil, but this occurs only during the agonic period, and is really due to the approaching dissolution and not to the effects of morphine; as long as the body is able to respond to the effects of drugs morphine leads to a contraction of the pupil. The effect upon the pupil does not occur when the drug is instilled into the eye, and is therefore of central origin. It is probable, but has not, so far as I know, been experimentally proven, that the contraction of the pupil is due to stimulation of the oculo-motor center.

Elimination.—After its absorption morphine is largely destroyed in the system, being oxidized to a comparatively inert substance known as dioxymorphine; from 25 to 50 per cent. of it, however, appears to escape from the body unchanged, partly through the urine, but chiefly through the glands of the digestive tract.

Therapeutics.—Opium, or its alkaloid morphine, is used for the following purposes: (1) To produce sleep; (2) to relieve pain; (3) to check certain secretions; (4) as a sudorific; (5) to relieve various respiratory paroxsyms; (6) to support the system in asthenic conditions.

As a somnifacient morphine is not to be recommended for routine use. In the first place, in the purely nervous types of insomnia—that is, when its wakefulness is not due to suffering—it is no more

efficient than are the somnifacients of the open-chain series, and it is vastly more dangerous, because of the liability of the formation of a habit, a danger which the physician should never lose sight of. It is, however, especially in the more obstinate types of insomnia, often of service, usually in conjunction with the aliphatic narcotics.

An an analgesic morphine is without a peer; indeed, without serious rival among therapeutic agents. So powerful is its influence in destroying the sense of pain that it is even used for the production of surgical anæsthesia, although the practice is not to be recommended. (See page 73.) Whenever the pain has resisted all other remedies the physician may always have a feeling of confidence in his reliance on morphine to conquer the sufferings. It matters not whether the pain is "functional," like neuralgia, or whether it is due to a broken leg or the invasions of a cancer, morphine, at least temporarily, will almost certainly alleviate it. It is, however, a remedy which is not to be used incautiously, especially when the pain is part of a chronic process or is liable to return at frequent intervals. In the first place, there is the ever-present specter of the morphine habit; in the second place, it is an agent to whose effects the patient becomes rapidly habituated, and whose power to relieve pain is comparatively slight, even if given in enormous quantities, in one who is tolerant of the drug; and, finally, its influence upon the digestive tract is sometimes powerful enough to seriously disturb the metabolic balance. For this reason in those conditions we may speak of as chronic pains the use of morphine should be postponed as long as possible by the use of the various other anodynes. When its employment is necessitated by the failure of other remedies, it is generally wise to combine it with some other analgesic, because, as noted above, the pain-relieving effects of analgesics are mutually enhanced by combinations.

Under the head of lessening secretions may be included the use of opium in three widely different diseases. In diarrhœas opium is probably the most potent and universally successful remedy that we possess. It acts partly by checking the intestinal secretions, but also partly by allaying peristalsis. In its use for this purpose, however, the same restrictions must be borne in mind as were pointed out concerning the use of tannic acid (see p. 76); namely, that the diarrhœa is often an expression of nature's effort to get rid of the irritant, and to check the symptoms without relieving the underlying condition is not proper treatment of the disease. In dysenteries it is of exceptional value, not only checking the diarrhœa, but through its sedative action relieving the pain and distress which tend to exhaustion of the patient's strength.

Under the head of its effects upon secretion may also be treated its employment in certain conditions of excessive secretion of urine, especially diabetes mellitus. How it acts under these circumstances is entirely a matter of conjecture, but, despite the denials of a few ultrascientific nihilists, there is no room for doubt that in certain

cases of diabetes opium will diminish not only the quantity of urine but also the quantity of sugar excreted, and, indeed, often aids in the restoration of the tolerance for carbohydrate foods. In this condition opium is certainly preferable to morphine, and, although many authorities have claimed to have obtained the same results from codeine, I do not believe that it is fair to conclude in any individual case that no benefit is to be derived from the opium until the entire drug itself has been tried. I know of no means of foreseeing in any individual case whether its use will prove beneficial or not, but it certainly deserves a trial in any case of diabetes which does not yield readily to dietetic measures. From the results which have been obtained from its use in diabetes mellitus has arisen its employment also in diabetes insipidus, and, although the evidence of its value in this latter condition is far less convincing, it is worthy a trial.

As a diaphoretic opium is nearly always employed in the combination with ipecac known as Dover's powders, the modern formula for which, however, differs from that originally prescribed by the famous old pirate, in that sugar of milk has been substituted for saltpeter. In conditions of not great gravity, as in the formative stages of a cold, this mixture in conjunction with the application of heat is very valuable, not only aiding elimination through its effects upon the sweat-glands, but, through the narcotic effect of the opium, relieving the discomfort of the patient.

In abnormal irritability of the respiratory center, such as certain forms of cough or the paroxysm of asthma, morphine is of much value. In cases of advanced heart-disease where there is great dyspnœa morphine used cautiously is often of service, not only because it relieves the distress of the air hunger and makes the patient comfortable, but because by so doing it enables him to obtain much-needed rest. Of course, in these diseases the drug must be used with great caution lest we add to the circulatory weakness the embarrassment of respiratory failure. Generally speaking, where the respiratory action of morphine is desired preference should be given to one of the allied alkaloids, such as codeine or heroine.

Physicians often fail to realize the amount of strength and energy which is used up by discomfort and suffering. In conditions of great feebleness, such as in the latter stages of asthenic fevers and in the very aged, the constant oozing of strength because of suffering may be sufficient to hasten a fatal issue. Under these circumstances the judicious use of morphine may prove a life-saving measure. It is doubtless this conservation of the physiological forces which has led to the superstition that morphine is a stimulant.

There are several more indications for the use of morphine which do not come strictly under any of the foregoing groups. For instance, in severe hemorrhage, especially in internal hemorrhages, it is of great value, not because it directly lessens the blood flow, but by its sedative action it allays the fright and excitement of the patient

and thus tends to prevent an excessive rise of blood-pressure, and also, by causing complete quietness, puts the body in the most favorable condition on nature's assistance in stopping the blood flow. In many cases of vomiting it is often of service, probably by blunting the perceptions of afferent impulses. In various convulsive disorders morphine has been widely employed, but is of very doubtful value; it is essentially a sensory, not a motor, depressant, and its control over the spinal cord is comparatively feeble.

Administration.—Wherever the drug is used as a narcotic—that is, to produce sleep or to relieve pain—morphine should always be given the preference over other preparations of opium as being less nauseating and less constipating. Ordinarily it is preferable to give the alkaloid by mouth, because of the associations in the mind of the ordinary layman with a hypodermic syringe, but, where a very quick or very powerful action is desired, subcutaneous injection may be employed. The combination which is so frequently employed with atropine is not one to be recommended, because the latter alkaloid increases the drying of the secretions, which is frequently so unpleasant a feature from the use of morphine. This combination has come into vogue because of the idea that atropine will guard against any possible respiratory depression from morphine, but the physician who is so reckless in his use of morphine that he has to guard against killing his patient with a physiological antidote is not fit to be trusted with so powerful a remedy. Moreover, if a corrective should be needed a much better one might be found in either strychnine or cocaine. In certain cases, however, such as the colic of gall-stones, the atropine, by its effect in relaxing spasm of unstriped muscle, enhances the analgesic action of morphine.

The old superstition that in pelvic disorders the suppository of opium acts more favorably than the drug given by the mouth has no basis in either fact or logic. It is to be remembered that any effect which opium may exercise in relieving the distress of a cystitis is due to its action upon the brain. The drug possesses practically no local effect, and if it did possess a local action its introduction into the rectum could not possibly affect the bladder. There is no condition in which the use of opium suppositories is a rational procedure, except in cases of vomiting where the stomach immediately rejects the drug, and in this instance it is better to use morphine hypodermically. In its influence over secretions, and especially in its effects upon the alimentary tract, opium is more powerful than morphine, and therefore it is generally given the preference in the treatment of diarrhœa.

Many persons cannot take opium on account of the very great secondary nausea and depression which it produces. It has been supposed that these disagreeable after-effects are due to the narcotine in opium; but this can hardly be, seeing that they often follow the use of the pure alkaloid, morphine. The deodorized tincture of opium agrees with some individuals better than any other prepara-

tion of the drug; and, as first pointed out by Da Costa, by giving a drachm of potassium bromide with twenty-five minims of it, the after-effects of the narcotic are often entirely avoided. Nitroglycerine in many cases will also lessen the gastric disturbance.

Children always bear opium very badly, but the idea that they should be given opium only in the form of paregoric is, to express it mildly, nonsense. So long as the dose is properly regulated and the apothecary has sufficient skill to weigh accurately morphine or any other opiate may be employed. As a general rule, it may be stated that for a child under eight years old the quantity of an opiate which may be administered safely is about one-half of that which would be proportional to its body weight. For example, if the dose of morphine for an adult is one-sixth of a grain, a child of three years old, weighing about one-sixth of the ordinary adult, should not be given more than one seventy-second of a grain of morphine.

Toxicology.—After the ingestion of poisonous doses of opium or its alkaloid morphine, there is a period, the duration of which is in inverse ratio to the dose ingested, in which there is a pleasant feeling of exhilaration and languor, with perhaps a slight increase in the rate and force of the pulse, and sometimes nausea and even vomiting. The condition of languor passes gradually into a complete sleep. The increase in the pulse-rate, if it occur at all, is only transient. The characteristic symptoms of opium poisoning at the stage when the case is usually seen by the physician closely resemble those of cerebral congestion; indeed, they are sometimes indistinguishable. The patient is asleep, but usually can be partially aroused by loud noises, shaking, cold water, and other means, but when left to himself immediately drops to sleep again; the pupils are contracted, the face flushed, sometimes slightly cyanosed, the skin is generally dry and warm, respirations are slower than normal, but usually fairly deep and regular. When the patient is aroused the respirations become more rapid and the skin regains almost at once its normal color; the pulse is slow, full, and strong. Death very rarely occurs during this stage. If the symptoms do not gradually ameliorate the patient passes into a condition of stupor and prostration, the sleep becomes comatose in character, so that it is frequently impossible to arouse him, the pupils are contracted almost to obliteration, the skin becomes cold and moist, the face is at once pallid and cyanosed, the respirations extremely slow and shallow and often interrupted by intervals of deathlike quiet, the pulse rapid and feeble, and gradually the patient dies with extinction of nearly all the vital functions, although the immediate cause of death is usually respiratory failure.

The most important points in the diagnosis are the equally contracted pupils, the character of the sleep, and the slowness of the pulse and the respiration.

Treatment.—Tannic acid has some value as a chemical antidote for opium, but the preference should always be given, where obtain-

able, to potassium permanganate, which acts not like tannic acid by forming a relatively insoluble salt, but through its oxidizing influence permanently destroys the toxicity of the morphine. The allegation, however, that potassium permanganate is capable of antidoting the morphine after its absorption is incorrect. In choosing an emetic the preference should be given to the locally acting drugs, as zinc sulphate and mustard, not only because of the promptness, but also of the certainty of their effect. Apomorphine in small doses may be employed, but not more than one-eighth of a grain hypodermically, as larger quantities may add to the depression.

To maintain respiration is the ultimate object of all the measures which are commonly undertaken for the purpose of arousing the system in opium poisoning. Unconsciousness in itself is of no moment, but as it deepens the sensibility of the respiratory centers grows less, and consequently the involuntary breathing is less rapidly or less perfectly performed.

For the purpose of keeping the patient awake various measures have been adopted, such as walking, flagellations, etc. Care should always be exercised, however, not to carry these useful measures to harmful extremes and perhaps add physical exhaustion to the natural prostration of the third stage. It is not uncommon in hospitals to see patients left black and blue from the excess of zeal and lack of judgment of hospital internes. An extremely valuable method of antagonizing the narcotic effects of opium with relatively no danger of injury to the patient is the use of the electric brush.

The cold douche is also an excellent method of rousing the patient and at the same time of especially stimulating respiration. The simplest method of application is to support the head and shoulders of a patient stripped to the waist over a common wash-tub, and to dash the water over the chest and head. The effect is much greater if ice-cold water and water a little hotter than the hand will bear (115° F.) be used in quick succession.

Respiratory stimulants are of great service; strychnine, cocaine, caffeine, and atropine may all be administered. Much better effects can be obtained from conjoint use of these remedies than from large doses of any one of them. Especially should a physician be warned against the use of overdoses of atropine. Caffeine is valuable not only as a respiratory stimulant, but also because of its effect upon the brain, tending to produce wakefulness. Occasionally in the advanced stages there is circulatory failure, in which circumstance digitalis and ammonia may also prove of value. If these measures fail to maintain a fair degree of respiratory activity, the use of artificial respiration should not be postponed. Inhalations of oxygen have also been used with apparently life-saving effects. The hypodermic or intravenous injection of physiological salt solution has also been recommended with the idea that it would aid in the elimination of the poison. Its value, however, is far from certain.

CODEINE.

The alkaloid codeine, which is found in opium in the proportions of about 0.5 per cent., may be regarded as a methyl-morphine. It can be formed artificially from morphine through the action of methyl iodide and alkalies. It is remarkable among the alkaloids for its comparative solubility, being dissolved by 88 parts of water and 1.6 parts of alcohol. The phosphate and sulphate are both official, although the phosphate is to be preferred as being more soluble. It is dissolved by less than 2½ times its weight of water.

The official salts of codeine are:

Codeina .....½ to 2 grains (0.03–0.12 Gm.).
Codeinæ Phosphas .....½ to 2 grains (0.03–0.12 Gm.).
Codeinæ Sulphas .....½ to 2 grains (0.03–0.12 Gm.).

Physiological Action.—Codeine in a general way resembles morphine in its effects, except that it is much less active, but especially so in its effect upon the cerebrum and on the intestinal tract.

As a somnifacient or analgesic codeine is practically useless. Its chief value in medicine is as a respiratory sedative in excessive cough and the like. A number of authorities assert that the value of opium in the treatment of diabetes is represented fully by the codeine.

DIACETYLMORPHINE.

In this artificial alkaloid, commonly called heroine, two hydroxyl groups of morphine are replaced by acetyl groups. The hydrochloride is official. It differs from morphine in that it is relatively feeble in its cerebral effects, and, according to Ott, in that it is depressant to the spinal cord. Its cerebral action is, however, more distinct than that of codeine, and, while vastly inferior to morphine as a pain-reliever, it has some anodyne properties. In the same way it is less constipating than is morphine, but has a distinct costive tendency. Its effect upon the respiratory center is both relatively and absolutely more powerful than that of morphine—that is, not only is its respiratory influence greater in proportion to its other effects, but it requires a smaller dose of heroine than of morphine to produce the same degree of depression of respiration.

A matter of some practical interest is the relation between the therapeutic dose and the toxic dose of these various alkaloids. According to the experiments of Impens, which have been confirmed by Morel-Lavalee, the least dangerous is heroine, because, although the fatal dose of heroine is smaller than the fatal dose of morphine, the proportion between the fatal dose and the therapeutic dose, using respiratory sedation as the therapeutic test, is greater. Codeine, although much less active than morphine, is relatively more dangerous —that is, as regards immediate results.

The most important use for heroine is as a respiratory sedative in whooping-cough, bronchitis, asthmatic paroxysms, cardiac dyspnœas, and the like. In the writer's experience it has proven itself at least the equal, if not the superior, of morphine in this group of cases, and it has the advantage over morphine in being less constipating and less nauseating. It is also occasionally of service in conjunction with the coal-tar anodynes for the relief of pain, although for this purpose it is greatly inferior to morphine. The same precautions are needed against the formation of a habit as with morphine.

The dose is from one-sixteenth to one-tenth of a grain.

ETHYLMORPHINE.

Ethylmorphine, or dionine, is an artificial alkaloid in which the hydrogen of the hydroxyl group of morphine has been replaced by an ethyl radical, and is, therefore, chemically closely related to codeine. Physiologically, it also resembles the latter alkaloid, but has a greater effect on the brain and intestines. The hydrochloride is official.

Therapeutic Uses.—As an internal remedy dionine has been used as a sedative to the respiratory center and as an analgesic. For the purpose of allaying cough it is inferior in power to heroine, but it is less liable to produce a drug habit and is also less constipating. For the purpose of allaying pain it seems to be superior to either codeine or heroine. Although much less efficient than morphine, the claim is made that it can be used for long periods of time without establishing either a tolerance or a craving. It has been also recommended as a sedative to relieve the discomfort consequent upon the withdrawal of the narcotic in those addicted to the opium habit. It has also been asserted to have the power of aborting acute coryza.

It is also a local important remedy in ophthalmology. One drop of a 2 per cent. solution of dionine placed upon the conjunctiva immediately produces smarting, free lachrymation, marked injection of the conjunctival blood-vessels, chemosis of the conjunctiva, and occasional swelling of the lid. In some cases its irritant action has been excessive, leading to œdema not only of the eyelids but of the neighboring tissues of the face. According to Wolffberg, the determination of serum to the eye brought about through the local effects of dionine is of great service, because afflux of the liquid carries with it an excess of phagocytes and the various anti-bacterial bodies of the blood. Whether or not this explanation of its *modus operandi* is correct, there is abundant clinical evidence as to its value in a number of ocular diseases. The detailed consideration of its use in ophthalmology belongs to text-books of that subject, but its indications in ophthalmic therapeutics may be stated in a general way to be a favorable influence in alleviating painful inflammations of the anterior portion of the eye and in relieving the distress incident to intra-ocular tension. It is useful, therefore, in such conditions as iritis, corneal ulcers, keratitis, glaucoma, and the like. There is also some evidence to show that it facilitates the absorption of various locally acting drugs, as atropine, physostigmine,

etc. According to Stiel it has a similar effect on the nasal mucous membrane and is a valuable remedy in atrophic rhinitis.

As a local remedy dionine may be applied in a 2 per cent. solution, or occasionally a small amount, say one-twelfth of a grain, of the powder may be dusted directly upon the ulcerated surface. Its dose internally is from one-fourth to one-half grain (0.015–0.03 Gm.).

CANNABIS.

Materia Medica.—The pistillate flowers of the hemp plant (*Cannabis sativa*), and various preparations made from this, have long been used in the East as narcotics under various names, such as *gunjah, churrhus,* and *hasheesh.* It was formerly believed that the narcotic property was found only in the East Indian variety of the hemp plant, but the experiments of H. C. Wood and of Houghton have demonstrated that the American plant possesses the same physiological properties, and the U. S. Pharmacopœia makes no distinction between them. While there is great variation of potency in different samples of cannabis, there is no proof that this is determined by climatic conditions.

Indian cannabis occurs in greenish-brown compressed masses markedly coherent from the large amount of resinous exudate. It has a peculiar narcotic odor and bitterish and somewhat acrid taste.

Various substances have been announced as the active principle of cannabis. Fraenkel asserts that the *cannabinol* of Wood, Spivey, and Easterfield is inert, and should be known as *pseudo-cannabinol,* the name cannabinol being retained for a distinct substance which he, Fraenkel, has isolated and found to be active.

Official Preparations:

Extractum Cannabis	⅛ to 1 grain (0.01–0.06 Gm.).
Fluidextractum Cannabis	1 to 4 minims (0.06–0.25 mil).
Tinctura Cannabis (10 per cent.)	10 to 20 minims (0.6–1.2 mils).

Physiological Action.—Cannabis seems to be limited in its action almost solely to higher centers of the nervous system. In man the first effect is upon the brain, in which it produces a peculiar disturbance of intellection, with great excitation of the imaginative functions of the brain followed by drowsiness. There is also even in man evidence of some depressant action upon the spinal cord, as shown by muscular weakness and diminished reflex activity. There is even in the early stages of the action of the drug a marked obtunding of the sense of pain.

In the dog the earliest manifest action of the drug consists in some motor inco-ordination so that the animal walks as though intoxicated and later shows distinct weakness of the hind legs, with diminished reflexes and drowsiness. In the frog there is a loss of reflexes with apparently a condition of partial anæsthesia.

Although it is asserted that large doses of cannabis produce some quickening of the pulse and occasionally dilatation of the pupil, the effects of the drug upon any of the vital functions are extremely

feeble, and enormous quantities can be taken without fatal results; in fact, I know of no fatal case of poisoning on record.

Therapeutics.—Cannabis indica is used chiefly for the relief of pain, especially of neuralgic character, although it sometimes will palliate even pain of organic origin. It is also at times of service for quieting conditions of restlessness and general discomfort—for instance, in neurasthenia—and to relieve the distress of the latter stages of incurable diseases, especially advanced phthisis. More rarely it is used as a mild somnifacient.

The great obstacle towards the more common use of this drug is the uncertain quality of the preparations upon the market. Not only is the substance as it enters this country often worthless, but a preparation even if originally active deteriorates with great rapidity. The only way to obtain an effect from it is to give it in ascending doses until there is some evidence of physiological action.

Toxicology.—The symptoms produced by large doses of cannabis indica are almost purely of a mental character, and they will vary greatly according to the individual. The most characteristic of them is the loss of the sense of time. A minute seems like an hour. This peculiar disturbance is very possibly due to the rapidity of the mental pictures, which are generally pleasant in nature, although sometimes associated with a sense of fear.

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Nothnagel ..... V.A.P.A., lxxxix, 2.
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Fuchs ..... W.K.W., 1902. (Dionine.)
Hinshelwood ..... B.M.J., 1906, i, 1098. (Dionine.)
Impens ..... A.G.P., 1899, lxviii, 527.
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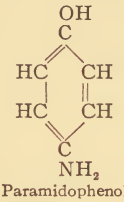
Wood, Easterfield and Spivey Journ. Chem. Soc., lxix, 539.

COAL-TAR ANALGESICS.

The second group of anodynes includes a number of derivatives of phenol. Phenol itself is but feebly analgesic, and is too highly poisonous to be practically useful for this purpose. Salicylic acid, however, has marked analgesic properties, although its use has come to be limited chiefly to a special group of cases. By the introduction of an amine into the phenol molecule the analgesic activity of the radical is greatly increased, so that for practical purposes nearly all of the anodynes of this series are derivatives of para-amido-phenol.

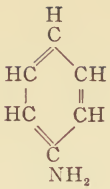


Paramidophenol.

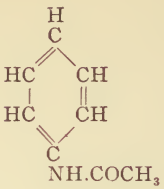
Within recent years an enormous number of these compounds have been invented by ingenious chemists and marketed by enterprising manufacturers. Since they are all manufactured from benzene, which is in turn derived from coal-tar, they are spoken of as the coal-tar anodynes.

A very remarkable and totally inexplicable fact is that all of this group of remedies not only lower the pain perception, but also lessen febrile temperature; moreover, their relative power as analgesics seems to be about the same as their relative power as antipyretics. Why there should be a relation between the abolition of pain and the abolition of fever, we have no idea.

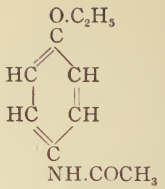
As has been stated above, those compounds owe their activity to the formation of paramidophenol in the system. It is important to note, however, that the derivatives of aniline (phenylamine), which contains no hydroxyl group, exercise the same influence and, indeed, are among the most powerful of this group of remedies. This is due to the fact, however, that they are oxidized in the system and appear in the blood as a phenol. The action of the simpler compounds is too brusque for practical purposes; that is, if sufficient of the remedy is used to bring out its therapeutic action it is liable also to produce toxic effects. By the introduction of certain side groups of the fatty acid series the toxic power is greatly reduced without seriously lessening their therapeutic efficiency, probably because these complex molecules must be slowly broken down in the system and the active paramidophenol is therefore liberated only gradually. The safety appears to vary, at least to an extent, vary proportionately to the complexity of their molecules; thus, acetanilid is less toxic than aniline, and acetphenetidin is less poisonous than acetanilid.



Aniline.



Acetanilid.



Acetphenetidin.

Antipyretic Action.—The temperature of the body is the result of an equilibrium between the amount of heat generated in the system through chemical activity and the amount given off through respiration and radiation from the skin. It is evident that if the generation of caloric be diminished and heat dissipation be unaffected,

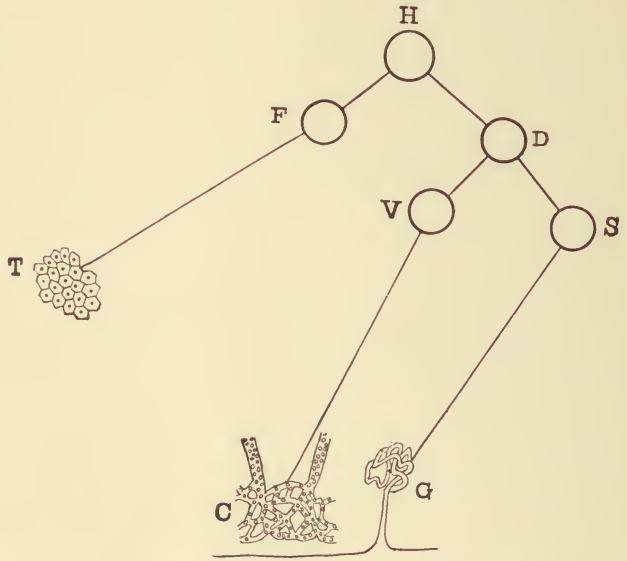


Fig. 13.—To show how drugs may affect body temperature. H, Heat-regulating center. F, Center for heat formation. D, Center for heat dissipation. V, Vasomotor center. S, Center for sweat-glands. C, Capillary blood-vessels in the skin. G, Sweat-gland. T, Tissue cells. Drugs may lower body temperature by diminishing chemical activity in T; or by increasing heat dissipation through dilatation of the skin capillaries or greater secretion of sweat.

or if radiation be increased and formation not, the temperature of the body will fall. As a matter of fact, however, the temperature of the body remains constant, because, when either of the thermic functions is affected, there is a compensatory regulation of the other; for example, when a man is placed in a cold bath there is a marked increase in heat elimination, but the temperature does not fall, because there is a corresponding increase in heat formation.

A number of attempts at an elucidation of the mode of action of antipyretic drugs have been made by studying the relation between

heat formation and heat dissipation. The results of these studies have been so unharmonious that it is impossible to escape the conclusion that the action of these drugs in fever is not a direct one on either the chemical processes or the radiation of heat. Wood, Reichert, and Hare found that in dogs antipyrine lessened both heat formation and heat dissipation, although the diminution in the former function was the more marked and the body temperature fell; similar results were obtained by Evans on the rabbit. In the experiments of Martin with antipyrine, on rabbits, there was in all except one instance an increase of heat elimination, with sometimes a greater and sometimes a lesser formation of caloric. Gottlieb, experimenting on rabbits, reached the conclusions that antipyrine lowered temperature solely by increasing heat radiation and that quinine acted by diminishing heat production. Perhaps the most elaborate of these studies are those of Stuhlinger. He found that in rabbits in which fever had been caused by the injection of pyrogenic bacteria, antipyrine increased both the amount of heat produced and the amount dissipated, and that the fall of temperature was due to the disproportionate increase in heat dissipation; in guinea pigs, on the other hand, there was a lessening of heat production and, to a smaller extent, also of its elimination. His experiments with quinine, although not so numerous, indicated a similar difference in the response of the two animals to this drug.

In view of the contradictory results which have been obtained by different investigators and under varying conditions, the only just conclusion would seem to be that the action of the antipyretics in fever does not depend on their influence on either the chemical processes of the body nor yet on the mechanism for the radiation of excessive caloric, but that they so affect the thermo-regulator center that it exercises its regulating influence at a lower temperature than before the administration of the drug. It must be remembered that there is in febrile states the same tendency to maintain the temperature of the body at a constant level, although a higher one, that there is in the normal animal, and, while the thermo-regulator mechanism is generally less prompt in its response, it is not destroyed. By increasing heat dissipation in fever—as, for instance, with the cold bath—while the temperature of the body may be temporarily reduced, it always tends to return to its original abnormal height. In the same way the provocation of profuse diaphoresis with chemical agents, which must greatly increase heat dissipation, does not correspondingly reduce the temperature, because the loss of heat is made up by the action of the thermogenic center. In other words, the difference between a febrile man is not so much that the thermo-regulator center is not acting, but that it tends to maintain a constantly higher temperature.

This disposition for the maintenance of the temperature at the same height is not destroyed by the antipyretics: it is merely modified

in such a way that the height is a lower one. It may be that they act by benumbing the heat center to the pyretic impulses of the toxins which are the direct cause of the fever.

Therapeutic Uses.—The coal-tar derivatives are used for three purposes—to relieve pain, to lower febrile temperatures, and for the relief of certain motor disturbances.

In their analgesic effects these agents must be sharply differentiated from the opiates. The subjective sensation of pain may arise either from irritation of the peripheral sensory nerves as the result of conditions originally external to the nervous system itself —for example, a local inflammation—or they may arise from conditions within the nervous system, as in neuritis or neuralgia. As stated previously, morphine is equally efficacious in both these types of pain; on the other hand, the coal-tars—although when given in large dose having some influence—are vastly inferior in allaying those pains which are the result of conditions outside of the nervous system; but when the cause of the pain is found within the nervous system itself, and especially when the suffering is of functional origin—that is, when there is no demonstrable organic lesion in the nervous system—they are powerful analgesics. The aniline derivatives, therefore, find their greatest usefulness in such conditions as migraine and neuralgia, but they are also of service in the pains of organic diseases of the nervous system, such as locomotor ataxia and neuritis. In the pains of extra-neural origin, such as are seen in local inflammatory conditions in operable cancers, etc., while themselves of but relatively feeble power, in some way they enhance the action of the opiates, so that by combining morphine with acetphenetidin, for instance, smaller doses are required than if the alkaloid was used alone.

The question of the relative value of antipyretic drugs or the cold bath for the reduction of excessive temperature in infectious diseases is one to which at present a positive answer cannot be given. So far as our present knowledge goes, the antipyretics produce greater disturbances in the general functions of the body than is caused by what we may call the mechanical abstraction of heat; further, the fever process itself is a disturbed condition of nutrition which is by no means thoroughly comprehended. In the administration of an antipyretic drug we are attempting to modify for the better a morbid process of whose real nature we are ignorant, by the use of a powerful drug of whose action we do not have definite knowledge. The use of antipyretics is at present empiric, and in our lack of knowledge the cold bath would seem to be a safer remedy. The greater convenience of these drugs, however, exerts a constant pressure for their use by the physician, and little by little confidence in them seems to be growing. One of their most serious disadvantages is their occasional inexplicable violence of action. The temperature falls so rapidly and so greatly at times, even decidedly below the

norm, that the heart, suddenly deprived of the stimulating effect of heat, is greatly depressed and collapse may result. This depressant influence is more likely to occur in the prolonged fevers, as typhoid, especially in the latter stages, when the general strength has been reduced by the continued drain of the infection. Our present information would indicate that in minor cases of fever, such as measles and influenza, the antipyretic is often superior to the cold bath because of its greater ease of application, but in severe or prolonged infections, especially when there is a tendency to adynamia, the best results are to be achieved with the cold baths, using the chemical antipyretics, if at all, merely as adjuvants for the purpose of assisting and prolonging the influence of the bath. Whenever used to reduce the temperature they should be given in relatively small doses, because of the possible danger of excessive action.

ACETANILID AND ACETPHENETIDIN.

Materia Medica.—*Acetanilid, antifebrin,* or *phenylacetamide,* is an aniline in which one atom of hydrogen has been replaced by the acetyl radical, or it may be considered as an ammonia in which one atom of hydrogen is replaced by phenol and another atom by acetyl. It is a white, crystalline substance, entirely without odor, having a bitter, mildly piquant taste. It is soluble in one hundred and seventy-nine parts of water and in two and a half parts of alcohol.

Acetphenetidin, or *phenacetin,* an acetyl derivative of para-amidophenol, crystallizes in tasteless, colorless needles, almost insoluble in water, soluble in alcohol. It represents about 75 per cent. as much paramidophenol as the same quantity of acetanilid would.

Official Preparations:

Acetanilidum .....3 to 6 grains (0.2–0.4 Gm.).
Acetphenetidinum—Phenacetin .....5 to 15 grains (0.6–1.0 Gm.).

Physiological Action.—*Nervous System.*—The action of these drugs on the heat-centers has already been sufficiently described; they are also feebly depressant to the motor centers, in the lower neuron producing, if used in large enough quantity, a diminution of reflex activity, and also exercising a feebly depressant influence upon the respiratory center. Although Boki asserts that when brought in local contact acetanilid paralyzes the peripheral endings of the motor nerve, such effect cannot be seen even in the frog from its internal administration.

Circulation.—There is a widespread superstition among clinicians that these substances are depressant to the heart even in therapeutic quantities, a belief for which there is neither pharmacological nor clinical evidence, for, although Hale has shown that in doses of ten centigrammes per kilogram of body weight, such a quantity, corresponding to over 100 grains for a man, cannot be taken as any

criterion of their effects in therapeutic doses, and I have found that in the dog acetphenetidin, even in doses of one-half gramme per kilo, has practically no influence upon the blood-pressure.

The reported cases of sudden collapse which have followed the use of acetanilid or acetphenetidin have nearly all occurred either when the drug was being given in large doses as an antipyretic or in persons who had been taking it for long periods of time. In the first group of cases it is probable that failure of the circulation was due to the sudden fall of temperature, and in the second group of cases the results have depended probably upon degenerative changes in the heart muscle due to the effect of the drug upon the blood. Idiosyncrasies against these remedies, however, appear to be not common, and occasionally alarming symptoms follow the exhibition of moderate doses.

When used in large doses, especially over long periods of time, these drugs lead to the formation of methemoglobin. There are probably other and earlier changes in the blood caused by these drugs which are not, however, at present clearly understood.

Therapeutics.—The use of these drugs as antipyretics and analgesics has already been considered. It may be added that acetanilid is sometimes employed as a mildly antiseptic desiccant dusting-powder to small ulcers. Cases of poisoning have followed the too free external use of acetanilid.

COAL-TAR DERIVATIVES.

Arduin.....Thesis, Paris, 1885.
Batten and Bokenham.....B.M.J., 1889, i.
Cerna and Carter.....New Remedies, 1892.
Gottlieb.....A.E.P.P., 1889, xxvii; A.E.P.P., 1891, xxviii, 167.
Hare.....T.G., 1887, xi.
Ott.....J.N.M.D., 1888, xv.
Riethus.....A.E.P.P., 1900, xlvii, 240.
Stengel.....J.A.M.A., xlv, 243.
Stengel and White.....U.P.M.B., 1903.
Stewart.....J.A.M.A., 1905, xliv, 1725.
Stuhlinger.....A.E.P.P., 1899, xliii, 167.
Wood, Reichert and Hare.....T.G., ii, 803.
Wood, Jr., and Wood.....U.M.M., July, 1900.

ANTIPYRINE.

Materia Medica.—Antipyrine was one of the earliest of the coal-tar synthetics to be introduced into medicine. It is phenyl-dimethyl-pyrazolon, and occurs as a colorless crystalline powder with a bitter saline taste. It differs from most of the other coal-tar analgesics in that it is freely soluble in both water and alcohol.

Physiological Action.—Antipyrine appears to differ from the previously-considered drugs of the coal-tar series in that it does not yield paramidophenol in the system. It probably acts as antipyrine, although eventually it undergoes chemical change in the body, being eliminated chiefly as a compound of oxyantipyrine with glycuronic

acid. Because of its free solubility in water it is more promptly absorbed than many other remedies of this class.

Nervous System.—Antipyrine, while powerfully depressant to the pain-perceiving mechanism, in proper dose exercises a distinct stimulant influence upon many portions of the central nervous system; thus in the frog, and probably also in the lower mammals, if given in toxic quantities it is capable of producing severe convulsions of a spinal type. The convulsions, however, as seen in the warm-blooded animals seem to be due, at least in part, to an action upon the motor area of the brain as well as on the spinal centers. Eventually, if the dose has been large enough, there is produced a condition of complete paralysis of the motor system. There is also evidence that there is the same sequence of primary stimulation and secondary depression in the activity of the special senses.

Circulation.—It seems proven beyond cavil that moderate doses of antipyrine cause an increase in the arterial pressure. The cause of this rise has not yet been fully determined, but it would appear that it is due, at least in part, to a direct influence upon the heart, but probably also to a similar influence upon the vascular muscles. After toxic doses the blood-pressure falls, due to a depressant action on the whole circulatory tract. Like the other coal-tar analgesics, antipyrine when used freely may give rise to methemaglobinemia.

Local Action.—Antipyrine, when brought in contact with mucous membranes, exercises a marked local effect, paralyzing the peripheral endings of the nerves, especially of the sensory nerves, and causing a contraction of the arterioles. It also has a distinct, although feeble, antiseptic effect.

Therapeutic Uses.—The use of antipyrine as an analgesic and antipyretic has already been sufficiently considered. It can only be pointed out that its action is more prompt than either acetanilid or acetphenetidin. It appears to exercise a greater effect on the skin circulation and the sweat-glands, and is by many believed to be more likely to cause collapse than the more slowly acting drugs.

Antipyrine has also been used to a large extent in the treatment of various spasmodic disorders, especially whooping-cough and epilepsy. How it does good in these conditions we have absolutely no information, but the clinical evidence is strong that it is of benefit.

Besides its internal use, antipyrine is a valuable local remedy both for its local anæsthetic effect and its vasoconstrictor action. It is widely used in the treatment of acute and subacute congestions of the nose and throat.

DRUGS USED TO DEPRESS THE SPINAL CORD.

In the anterior horn of the gray matter of the spinal cord are certain cells which send out through the nerve-trunks contractile impulses to the voluntary muscles. These spinal centers do not seem to be able to originate motor impulses, but must be activated by

stimuli received either from the motor cells in the cerebrum or from the sensory ganglia of the cord. We have, accordingly, two sets of muscular movements—the voluntary movements, which begin in the psychomotor area of the brain and pass down the spinal cord to the motor cells in the anterior horn, and the reflex movements, which begin as the result of an irritation of the sensory nerve, passing up along the afferent nerve-trunks and through the sensory ganglia to the spinal motor cells. It is evident that the transformation of the convulsive impulse into muscular movement will depend upon

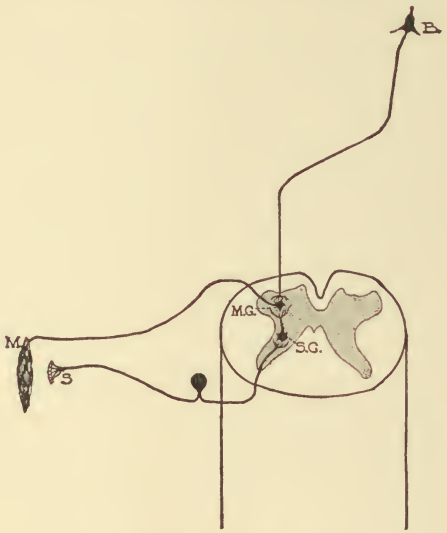


FIG. 14.—Diagram to show how drugs may stop convulsions. B., Motor cell in brain. M.G., Motor ganglion in the anterior horn of the spinal cord. M., Muscle. S., Peripheral end of sensory nerve. S.G., Intermediate (sensory) ganglion of the spinal cord. The bromides prevent impulses reaching the motor cells of the cord by paralyzing S.G.; chloral hydrate, physostigmine, and the nitrites paralyze M.G.; lobelia, conium, and curare paralyze the nerve-endings in the muscle.

the physiological integrity of the motor cells in the cord, the efferent nerves, the muscles, and, in the case of the reflex convulsion, also upon the activity of the afferent nerves and the receptive ganglia. Theoretically, it is possible to control convulsions by paralyzing any of the structures involved, but practically we are limited, at least as regards general spasms, to those substances which act centrally; that is, either upon the brain or spinal cord.

A motor nerve paralyzant will destroy the conductivity of the phrenic nerve along with the other nerves of the body—indeed, the experiments of Muto with lobelia and conium would indicate that the phrenic nerve is even more susceptible than other motor nerves—and lead to paralysis of the diaphragm and consequent asphyxiation. It is evident, therefore, that those substances which allay convulsions by acting upon the efferent nerves are useful only when they can be

applied locally. As regards the peripheral sensory nerves, while there is no theoretic objection to them, the practical fact is that we know of no substance which paralyzes the peripheral sensory nerves without producing serious disturbance in other parts of the body.

A paralysis of the motor cells in the cord will prevent both voluntary and reflex movements, whereas a paralysis of the sensory ganglia, while checking all reflex action, will not hinder voluntary motion, as the pathway from the brain to the muscle is intact. Two sorts of convulsions are known—those which are due to hyperactivity of the motor area in the brain, commonly called cerebral or epileptiform convulsions, and those which are due to abnormal irritability of the reflex centers in the cord, commonly called spinal convulsions. It is apparent that a drug whose action is upon the motor centers of the cord will be useful to check all types of convulsions, both cerebral and spinal, but that one whose action is upon the sensory apparatus is useful only in the spinal convulsions. The depresso-motors may, therefore, be divided into two groups, according as to whether they act upon the motor or sensory side of the spinal cord. Among the latter the only one of clinical importance is the salts of hydrobromic acid. The most important of those which depress the motor centers of the cord are the nitrites, physostigmine, and chloral. The last named has already been considered.

Certain motor nerve paralyzants are of importance, either because of their action upon other structures of the body, or else from their toxicological relations, and will, therefore, be considered in this chapter.

Besides those agents which are mentioned in this chapter, the following drugs which are considered elsewhere in the book are clinically useful for the relief of convulsions: chloral hydrate, veratrum, chloroform, and the nitrites.

BROMIDES.

Materia Medica.—Hydrobromic acid is recognized by the Pharmacopœia in the form of a ten per cent. solution. This is a colorless, odorless liquid with a strongly acid taste. On account of its irritant action upon the stomach it is comparatively little used in the form of the acid itself, but is chiefly employed in the form of one of its salts. Of these there are official, ammonium, calcium, lithium, potassium, sodium, and strontium bromides.* These all occur in the form of colorless or white crystals of a bitterish salty taste, freely soluble in water and, with the exception of potassium bromide, all soluble in alcohol. All except the potassium and ammonium salts are more or less hygroscopic.

Incompatibilities.—The hydrobromides of many of the alkaloids are insoluble in water, and therefore care should be observed in com-

* Zinc bromide is also official, but has no useful place in therapeutics.

bining bromides in solutions containing alkaloids. Oxidizing agents liberate free bromine from the salts of hydrobromic acid. The bromides are also incompatible with spirit of nitrous ether, with silver nitrate, and with calomel.

Official Preparations:

Acidum Hydrobromicum Dilutum (10 per cent.)	1 fluidrachm (4 mils).
Ammonii Bromidum	10 to 60 grains (0.6–4.0 Gm.).
Calcii Bromidum	10 to 60 grains (0.6–4.0 Gm.).
Lithii Bromidum	10 to 60 grains (0.6–4.0 Gm.).
Potassii Bromidum	10 to 60 grains (0.6–4.0 Gm.).
Sodii Bromidum	10 to 60 grains (0.6–4.0 Gm.).
Strontii Bromidum	10 to 60 grains (0.6–4.0 Gm.).

The bromic ion is not so active but what sufficient quantities of the bromides may be administered to obtain some evidence of the effect of the base, so that, while these salts are similar in their actions, they are not identical; the differences in their effects will be pointed out later.

Physiological Action.—The bromide ion is a depressant to all forms of protoplasm, but has an especial attraction for the central nervous system. It is a protoplasmic depressant, being remarkable in that while comparatively small doses interfere with the vital manifestations of cellular activity yet relatively large doses do not destroy viability.

Nervous System.—As mentioned above, in sufficient quantities the bromides are depressant to all the nerve-centers and probably also to nerve-endings. Its value in medicine depends upon the order of susceptibility of the nervous system.

In the frog, after an administration of a moderate dose of a bromide, there is a loss of reflex action at a time when voluntary motion persists. The maintenance of volitional power shows that the motor tract from the brain to the muscle remains intact at this stage of the poison. The action of the drug, therefore, must be upon the sensory portion of the nervous system. If by ligation of an artery of one leg the access of the poison to the peripheral nerve is prevented it is found that the reflexes disappear as rapidly from the protected side as from the unligated leg, showing that the action of the drug is central. After larger doses there also occurs a loss of voluntary movement, but whether this is due to an action upon the motor centers of the brain or upon the motor side of the spinal cord is not certain; probably both are involved. In the frog, therefore, the first cells affected are the receptive ganglia of the spinal cord, then the motor area of the brain and cord. After sufficient dose there is probably also some late effect on the peripheral sensory nerves.

In man the order of involvement is somewhat different, because the more highly developed cerebrum in the human being is more

susceptible to the action of the drug. Its effect upon the brain, however, is chiefly upon the psychomotor area. Loewald has found that ordinary doses of bromides produce comparatively insignificant changes in intellectual activity except to protect the thought from disturbing extraneous factors. After sufficient doses it also depresses the sensory apparatus of the spinal cord, as shown in diminished reflexes. It is not possible in human beings to obtain an action upon the peripheral nerves.

An observation made by Albertoni, and of much interest from the standpoint of the clinical utility of the drug, is that although the single dose of a bromide diminishes markedly the irritability of the motor zone of the cerebral cortex the effect is much more pronounced when the drug has been given for a long period of time than after a single dose, however large.

Circulation.—The idea which was at one time held that the bromides were depressant to the circulation depended upon the fact that the earlier investigations were made exclusively with the potassium salt, the depressant effect being due to the potassium rather than to the bromic ion. There is no evidence that in ordinary dose the bromic ion exercises any distinct influence on the circulation.

Nutrition.—The symptoms which are produced by the continual use of bromides in large doses show that they have a powerful influence on the nutritive processes of the body, the precise nature of which is, however, at present not clearly understood. The harmonious researches of Chittenden and Culbert and of Schultz seem to show that the bromides increase the output of nitrogen, but diminish the amount of phosphorus eliminated.

Absorption and Elimination.—The bromides are easily diffusible salts and therefore absorbed with a fair degree of rapidity. Their elimination, however, is comparatively slow, so that they tend to accumulate in the system when used over long periods of time. They escape from the body through every possible channel of elimination, having been found not only in the urine and intestinal secretions, but also in the tears, saliva, and even in the pustules which follow their free use.

Therapeutics.—The bromides are used in medicine for four purposes: (1) To relieve cerebral convulsions; (2) to relieve spinal convulsions; (3) to relieve pain; (4) to quiet nervous excitement.

Under the first of these headings may be considered the use of bromides in epilepsy, although the mode of their action in this disease must be uncertain until we have some idea of the essential pathology of the condition. However they act, it is certain that they offer the most valuable symptomatic remedy that we have in this condition. In using the bromides in epilepsy three facts should be borne in mind: First, that their effects are not curative; second, that the motor centers in the brain are the most susceptible of all of the nervous system to the action of the drug; and, third, that when used for considerable periods of time they not only tend to accumulate

in the system, but seem to exercise a degree of action which cannot be obtained from any single dose, however large. A practical deduction from the first of these facts is that their use must be continued ordinarily throughout the life of the patient. I have seen an epileptic who was absolutely free from any symptom of disorder for nearly three years seized with a typical epileptic paroxysm within two weeks after the withdrawal of the remedy. In rare instances, however, the patient may permanently recover under the prolonged use of the bromides. The fact that the motor cortex is peculiarly susceptible to the depressant action of bromine indicates that only relatively small doses are necessary. Rarely, except perhaps in the beginning of a treatment, is the use of more than sixty or ninety grains in the twenty-four hours required, and less will often suffice. Much harm has been done to epileptics by the enormous quantities of the drug which are sometimes employed.

In the treatment of tetanus the bromides are among the most valuable remedies we possess. The persistency of their action makes them peculiarly valuable. They must be given in large doses; a simple rule which is generally applicable is that less than 240 grains in the twenty-four hours is a waste of drug. In strychnine poisoning the slowness of their action greatly lessens the value, but used in conjunction with more rapidly acting depressants they are of service.

As analgesics the bromides are of much value as adjuvants to the more powerful remedies, especially in the treatment of neuralgias. The combination with morphine is particularly valuable, because they not only enhance the anodyne effect of the opiate, but lessen its tendency to nauseate.

Under the fourth head of quieting excitement, the bromides have been used and abused to an enormous extent in all kinds of conditions, for many of which they are absolutely unsuitable. It is to be noted that it is only in very large quantities that they affect the intellectual centers, and moderate doses can act only through depression of the sensory tracts of the spinal cord. In conditions of spinal excitement, such as sexual disorders, they are of great service. In conditions of cerebral excitement, such as hysteria, although very widely used, unless given in enormous dose they are of comparatively little value. Their use as somnifacients deserves some more detailed consideration. While they have a certain value in some types of wakefulness, their mode of action is essentially different from that of the somnifacients proper. They do not in the dose ordinarily employed directly tend to produce sleep, because they do not depress the higher cerebral centers, but in fairly large quantities, by obtunding the perceptive faculties, they shut out those minor irritations which tend toward wakefulness. It is as though we had put our patient in a quieter room and a more comfortable bed because of their depressant influence upon the reflex centers. The bromides are frequently of use in certain forms of vomiting. Thus I have found

them of great service for the prevention of sea-sickness, and they are also worthy of a trial in the excessive vomiting of pregnancy.

Concerning the use of bromides in neurasthenia there is considerable difference of opinion. Many authorities believe that, although they may be symptomatically useful, yet by interfering with the metabolism of the central nervous system they prevent permanent recuperation. Personally I believe that their effect upon the metabolism of the nervous system is a favorable one. The fact that the output of phosphorus is lessened by them tends to show that there is a diminution in the breaking down of the nerve protoplasm, and my own experience is that their use for considerable periods of time is beneficial rather than harmful in cases of nerve weakness.

Choice of Bromide.—The action of the bromide is to a certain extent modified by the base with which it is combined. A knowledge of the effects of these bases is all that is necessary to guide us in the choice of bromide in any particular case. Potassium is a depressant not only to the circulation but also to the central nervous system (see page 31), and is therefore the most powerful of the bromides, but is liable, also, when used freely, to affect the circulation; it seems, also, more irritant to the stomach than other salts. The ammonium radical is stimulating in its effect upon the spinal cord (see page 194), and therefore this salt is less useful as a spinal depressant than other bromides. Also, the activity of the bromides probably bears a relation to the percentage of bromine in their composition; it is interesting to note, therefore, that calcium bromide contains eighty per cent. of bromine; sodium about seventy-seven per cent.; potassium salt about sixty-seven per cent., and the strontium bromide, sixty-five per cent.; a fluidrachm of the dilute hydrobromic acid is equivalent to about eight grains of sodium bromide. For general purposes the sodium bromide is probably the salt of preference, although frequently the best results are obtained by combining several of the bromides.

When the bromides are used in chronic conditions it must be borne in mind that on account of their comparatively slow elimination there is a marked tendency for them to accumulate in the system and that, therefore, when used over long periods of time they must be given in much smaller doses than when used in a single dose. While it is perfectly safe to give one or two drachms of sodium bromide or even more at a single dose, in diseases of prolonged duration, such as epilepsy, this quantity cannot be exceeded in the twenty-four hours without danger of unpleasant symptoms.

On account of the irritant action upon the stomach the bromides should always be given well diluted.

Toxicology.—So far as I know, no fatal case of acute poisoning by potassium bromide is on record. In a case reported by Dougall an ounce and a half taken within twenty-four hours was followed by coma, with weak pulse, cold extremities, temperature 96.8° F., total

abolition of the reflex action, and general cutaneous anæsthesia, followed by excessive drowsiness interrupted by periods of talking delirium and by periods of rationality, the symptoms gradually subsiding during a fortnight.

From the continuous employment of large doses of the bromide, however, when it is taken with sufficient freedom to accumulate in the system, a conjunction of phenomena known as *bromism* arises. The cerebral symptoms are a sense of mental weakness, heaviness of intellect, failure of memory, partial aphasia, great somnolence, and depression of spirits. With these there may be decided impairment of the sensibility of the mucous membranes and of the skin, so that titillation of the fauces may be without effect, and, according to Puche, even heat applied to the skin calls forth no complaint; Huette has seen in some cases absolute anæsthesia of the sclerotic conjunctiva. The sexual function is abolished. There are also very generally fetid breath and an eruption of acne which may indeed be very severe. Of course, in any individual case of bromism many of these symptoms may be wanting; but when the use of the remedy is persisted in, they all at last become developed in an intense degree.

The symptoms of bromism usually disappear promptly with the withdrawal of the drug and leave no unpleasant sequelæ. Apparently the use of arsenic greatly lessens the inclination to acne, and it is frequently well, when using the bromides for long periods of time, to add one or two minims of a solution of potassium arsenite to each dose.

PHYSOSTIGMA.

Materia Medica.—This substance, commonly known as Calabar bean, is an irregular, kidney-shaped seed, about an inch in length and three-fourths of an inch wide, the product of the *Physostigma venenosum,* a perennial woody creeper of Calabar, Africa, where it has been used by the natives as an ordeal test for criminals, witches, etc., since time immemorial. It owes its activity chiefly to the alkaloid *physostigmine,* or *eserine.* E. Harnack and L. Witkowski have described a powerful tetanizing alkaloid, *calabarine,* which is sometimes abundant in commercial extracts of Calabar bean. It is probably a decomposition product from physostigmine. *Isophysostigmine,* according to Ogiu, is similar in its action to physostigmine, but more powerful. The U. S. Pharmacopœia directs that the drug shall contain 0.15 per cent. of alkaloids.

Official Preparations:

Extractum Physostigmatis .....1/8 to 1/4 grain (0.008–0.015 Gm.).
Tinctura Physostigmatis (10 per cent.).....15 to 30 minims (1–2 mils).
Physostigminæ Salicylas [Eserine Salicylate]..1/60 to 1/30 grain (1–2 Milligm.).

Physiological Action.—Physostigmine, like pilocarpine and muscarine, has a stimulant action upon the peripheral endings of the

autonomic nerves and is capable of causing all the changes in function which have been described under pilocarpine (see page 47). Although it is capable of increasing glandular secretion, as does pilocarpine, it is rarely used for this purpose in practical medicine because it exercises so powerful an influence on certain nerve-centers.

Muscular System.—Physostigmine has a marked effect on both striped and unstriped muscles. In large doses it causes a peculiar tremor of the voluntary muscles which is not due to any effect upon the nerve-centers, because it occurs after section of the nerve-supplying part. These tremors are abolished by curara, and, on the other hand, the paralytic effect of curara on nerve-endings may be, at least in part, overcome by physostigmine. It would seem, therefore, that the action was upon the peripheral endings of the motor nerve rather than upon the muscle substance.

Physostigmine markedly increases the peristaltic movements of the intestinal tract, even after destruction of Auerbach's plexus. According to Magnus, it differs in its effects upon the intestines from muscarine and pilocarpine, in that it increases not only the muscular tone but also the extent of the contraction waves, and in that its action is not overcome by moderate quantities of atropine.

Nervous System.—The effect of physostigmine upon peripheral nerve-endings is outweighed by its action upon the nerve-centers. In both the frog and the mammal it produces a loss of reflex activity, with eventually complete paralysis, by direct depressant action upon the motor side of the spinal cord; in the warm-blooded animal death is caused by arrested respiration.

Circulation.—The most marked change in the circulation after physostigmine is the slowing of the pulse, although after large quantities there is also an elevation in the blood-pressure. The slowing of the pulse is not prevented by previous section of the pneumogastric nerve, and is, therefore, of peripheral origin. Whether the action is upon the peripheral inhibitory mechanism or on the heart muscle cannot as yet be considered to be definitely proven, although our present evidence favors the view of an inhibitory stimulation. If, after its administration, the electrical current is applied to the pneumogastric nerve the amount of slowing of the pulse is much greater than would be caused by the same strength of current in the normal animal; in other words, there is an increase in the irritability of the vagus. According to Arnstein and Sustchinsky, even after the previous administration of atropine physostigmine is still capable of slowing the pulse, which would indicate that its effect was upon the heart muscle; but, on the other hand, Rossbach found that atropine completely abolished the effect of physostigmine upon the pulse-rate. The probable explanation of these facts is that there is an antagonism between the action of physostigmine and atropine upon the peripheral inhibitory mechanism, so that when the dose of atropine is small the physostigmine is able to overcome it and restore irritability to the vagal endings,

but that after a sufficient dose of atropine its paralytic effect cannot be overcome by the stimulant action of physostigmine; it must be remembered that eventually when both are given in large doses the paralyzing drug will always overcome the effects of a stimulating drug.

The rise of blood-pressure occurs after section of the spinal cord, and must, therefore, be due to an effect either upon the heart or the arterial muscles, including under this latter term the peripheral nervous apparatus contained in the arterial walls as well as the muscles themselves. The probabilities are that both heart and blood-vessels share in the stimulation.

These changes in the circulation are secondary to the other effects of the drug and, except possibly the slowing of the pulse, could hardly occur from the therapeutic use of the drug.

Eye.—When instilled into one eye physostigmine causes a contraction of the pupil on that side and not of the other; therefore, its action is peripheral. That the action of the drug is not upon the muscle substances is shown, first, by the fact that after section of the short ciliary nerves and degeneration of their terminals physostigmine is unable to affect the pupil, and also by the fact that while after small doses of atropine the pupil may be contracted by physostigmine it cannot be if the dose of the atropine is sufficiently large. The fact that small quantities of atropine may be overcome shows that the contraction is an active one and not a passive one, and we must therefore conclude that it stimulates the peripheral terminals of the oculomotor nerve.

Just as physostigmine excites the endings of the oculomotor nerve in the iris, so does it excite them in the ciliary muscle, and gives rise to a spasm of accommodation, or, after previous paralysis by atropine, tends to restore the power of accommodation.

Therapeutic Uses.—Physostigmine is used in medicine chiefly for three purposes—as a depressant to the spinal cord, as stimulant to the intestinal muscles, and to contract the pupils. As a motor depressant physostigmine is useful in the treatment of tetanus and strychnine poisoning. It is, however, a remedy of distinctly secondary value, and, while serviceable as an adjuvant to more powerful drugs, should never be relied upon to their exclusion. Its greatest value in internal medicine is as a stimulant to the intestinal muscles in paralytic forms of colic, but especially in chronic constipation in conjunction with cathartic drugs.

The instillation of a drop of a one-quarter to one-half per cent. solution of eserine sulphate into the eye is followed by strong contraction of the sphincter of the iris and by spasm of the ciliary muscle which adapts the eye for the near point. Its action begins in about one minute, usually reaching its maximum in from twenty to thirty minutes, and lasts from twenty-four to thirty-six hours. The intraocular tension is reduced, provided it has been raised above the normal point before the application of the drug. It is used by ophthalmologists:

First, to reduce abnormally high intra-ocular tension, particularly in glaucoma; second, to prevent or reduce prolapse of the iris after cataract extraction or from a perforating corneal ulcer; third, to limit the progress of deep ulcers near the margin of the cornea, because it is supposed to promote absorption through dilatation of the ciliary vessels and to check the sloughing process; fourth, to counteract the effect of the milder-acting mydriatics—for example, homatropine—especially in eyes in which their use has tended to raise intra-ocular tension; fifth, to overcome paresis of the ciliary muscle resulting from various diseases—for example, diphtheria, diabetes, syphilis. Eserine, too freely used, especially in hyperæmic eyes, is capable of causing slight iritis, the so-called eserine iritis.

BROMIDES.

Albertoni ..... A.E.P.P., xv, 256.
Chittenden and Culbert ..... S.L.C.Y.
Dougall ..... Gl. M.J., Feb., 1893.
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Greeve and Kruse ..... J.A.M.A., 1913, lxi, 271.
Schulz ..... Z.B., 1883, xix, 301.

PHYSOSTIGMA.

Arnstein and Sustchinsky ..... U.P.L.W., Theil, ii, 86.
Fraser ..... Tr. R.S. Ed., 1870, xxiv.
Loewi and Mansfeld ..... A.E.P.P., 1910, lxii, 180.
Magnus ..... A.G.P., 1905, cviii, 1.
Ogiu ..... Ther. Geg., 1904.
Schulz ..... A.P., 1898.

MOTOR NERVE PARALYZANTS.

Derived from pyridine are a number of alkaloids of very similar physiological action; these are piperidine,* coniine, lobeline, sparteine, and nicotine. While we do not know enough of the chemistry of curarine and gelseminine to assert positively that they belong to this group chemically, they so obviously do physiologically that they are here included with them.

The characteristic effect of these substances is to paralyze the peripheral ends of the motor nerves, although several of them have other actions more or less peculiar to themselves. A drug which lessens reflexes through an action upon the motor nerves is not therapeutically useful as an anticonvulsant, because of the effect upon the phrenic nerve, which nerve has experimentally been shown to be even more susceptible to the action of this group of remedies than other motor nerves of the body.

While these remedies are of little service as depresso-motors, some

* Piperidine is not used in medicine. It closely resembles coniine in its action, but is very much feebler.

of them have other actions on the system which give them a place in our materia medica, while others are of interest purely from a toxicological standpoint.

CURARA.

Under the names of curare, curara, woorara, etc., there comes into commerce a blackish extract from South America which is used by the natives as an arrow poison. This substance appears to be composed mainly of an extract derived from various species of the genus *Strychnos,* especially the *S. toxifera* and the *S. castelnæana,* mixed with various impurities. It contains several alkaloids, the

Fig. 15.—Diagram to show the paralysistic effect of curare on the motor nerve ends. The artery of the left leg is ligated so that when the poison is injected it reaches all parts of the body except this leg. Now if an electric current be applied to the nerve of the left (protected) leg a contraction of the muscle will follow, but if the nerve of the right (poisoned) leg be stimulated it does not cause a contraction of the muscle. The action of curare must therefore be on the peripheral ends of the nerve and not on the spinal cord.

most important of which is known as curarine, or sometimes as tubocurarine. This drug is of little or no value from the standpoint of practical therapeutics, but is of great importance to experimental physiology and pharmacology, and, therefore, deserves a word of mention.

Physiological Action.—When injected into the frog curara produces a condition of complete paralysis. If in this curarized frog a motor nerve is exposed and an electrical current applied the customary contraction of the tributary muscle fails to occur, although when the electrodes are placed directly on the muscle it will respond as normally.

If two muscle preparations are made and the nerve of one (A) and the muscle of the other (B) allowed to soak in a solution of curara, after a period of time it will be found that stimulation of the nerve of preparation (A) will be followed by a contraction of the muscle, but that stimulation of the nerve of (B) will not be followed by a contraction of the muscle, but when the muscle of (B) is directly stimulated it responds to the electrical current, showing that the drug does not affect the muscle substance. Since the contractility of the muscle is not lost and since the motor nerve-trunk is not affected it follows that the inability of the nerve to convey the impulses to the muscle must be due to an effect on some portion of the motor nerve within the muscle itself, either the so-called motor end plates or some theoretical myoneural junction.

Curara paralyzes the end plates of all motor nerves supplying striated muscle-fiber, except the heart, apparently in all vertebrate animals. It appears to have no influence on the peripheral endings of any other kind of nerves, for, while the question of whether it affects the sensory nerve-endings cannot yet be considered definitely answered, it is at present improbable.

In large doses curara also paralyzes peripheral ganglia, so that excitation of the pneumogastric nerves may fail to slow the pulse and excitation of the secretory nerves fail to increase glandular activity. There is also a reason for believing that large doses excite the central nervous system, but any such effect is completely hidden by the paralysis of the motor nerves.

CONIUM.

All parts of the *Conium maculatum,* or water hemlock, famous in history as the penal poison of the Greeks with which Socrates was killed, contain several derivatives of piperidine, of which the alkaloid coniine (propyl piperidine) is the most important. This umbelliferous plant is a native of Europe, but has been naturalized in the United States, and occasionally is the cause of accidental poisoning. The fruit was formerly recognized by the U. S. Pharmacopœia.

Physiological Action.—Coniine very closely resembles curara in its physiological effects, by far the most important action being a paralysis of the peripheral ends of the motor nerves. The cause of death in fatal poisoning is a paralytic effect upon the phrenic nerve leading to failure of respiration. In the account of the death of Socrates by the poison, loss of sensation was one of the symptoms which impressed itself upon the bystanders, and there is some scientific evidence that the drug paralyzes the sensory as well as the motor fibers, although the point can hardly be considered as yet definitely proven. The convulsions which are sometimes seen in late coniine poisoning are probably asphyctic in origin. These convulsions are possible because the phrenic nerve appears to be more susceptible to the action of the drug than the other motor nerves of the body.

After very large doses of conium there is a paralysis of several of the sympathetic ganglia, just as there is after curara.

Conium has been tried in chorea, in paralysis agitans, in whooping-cough, and in other diseases of similar nature, but is probably without value. In maniacal and hysterical excitement, the drug in full doses is said to produce a highly favorable condition of calm and relaxation; and in the treatment of the insane, conium is much used by some alienists.

The characteristic symptoms of conium poisoning are extreme muscular weakness, generally at first marked in the legs, sometimes attended by burning in the fauces and epigastrium, and nausea and vomiting. The pupils sooner or later dilate, amblyopia from paralysis of accommodation, diplopia from irregular weakness of the ocular muscles, and ptosis are almost universally present, and the voice may be weakened to a whisper or lost. Sensibility is maintained to the end. Free salivation or free sweating sometimes occurs.

The circulatory phenomena are very subordinate; though the pulse-rate may at first fall, later it becomes more rapid. Consciousness is usually preserved until the last, but may be lost in asphyxial coma some minutes before death, which results from paralysis of respiration.

The treatment consists in the immediate evacuation of the stomach and the exhibition of tannic acid—the tannate formed is, however, probably more or less poisonous—with the use of external heat and of internal stimulants: artificial respiration should steadily be maintained so long as there is the faintest indication of cardiac action. No physiological antidote is known; but strychnine and other respiratory stimulants should be used.

NICOTINE.

Tobacco was at one time recognized by the United States Pharmacopœia under the name of Tabaccum, but is now no longer used in medicine. Its active principle, nicotine, has a certain toxicological and scientific interest and, therefore, deserves some mention. Nicotine is a liquid alkaloid forming, however, crystalline salts, and intensely poisonous. In the rapidity of its effects it rivals, if it does not surpass, prussic acid. In Wormley's experiments a single drop placed in the mouth of a full-grown cat produced death within seventy-eight seconds. The quantity contained in smoking tobacco varies considerably, ranging from one and one-half to eight per cent.*

Physiological Action.—The most important effect of nicotine is

* The statement sometimes made, that tobacco smoke contains no nicotine, is certainly erroneous, and it is probable that the evil results which follow excessive indulgence in the habit are largely due to the nicotine. To what extent, however, the attraction is due to the nicotine is very questionable. It is probable that very little of the poison is absorbed in the ordinary methods of smoking.

upon the sympathetic ganglia, which are primarily excited, secondarily paralyzed. It has, however, also an effect upon the intestinal muscles. and in sufficient quantity is paralyzant to the motor-nerves. The action upon the sympathetic ganglia produces changes in a wide variety of functions, which can best be considered seriatim.

The injection of nicotine into the circulation produces a marked, but transient, elevation of the blood-pressure with slowing of the pulse; following this there is a fall in the pressure below the normal with a rapid pulse. The rise of pressure occurs after destruction of the spinal cord, and must, therefore, be peripheral in origin and, as the output of the heart is not increased, is the result of vasomotor stimulation. If in a rabbit the superior cervical ganglion on one side is extirpated and nicotine administered, it can be noted that the ear on the intact side becomes pale under the influence of the drug—showing constriction of the blood-vessels—while the ear on the side from which the cervical ganglion has been removed becomes flushed rather than pale; in other words, after the removal of the superior cervical ganglion the nicotine does not cause contraction of the blood-vessels, and since its action is not upon the vasomotor center it follows that it must be upon the sympathetic ganglia. During the stage of low blood-pressure the vessels will be found to be dilated, owing to a paralysis of these ganglia.

The slowing of the pulse is not prevented by previous section of the pneumogastric nerve and must, therefore, be peripheral, but is at once abolished by atropine. The action is, therefore, evidently on some portion of the peripheral inhibitory mechanism. During the stage of rapid pulse stimulation of the pneumogastric nerve with the electric current will not slow the pulse, showing that the inhibitory mechanism is paralyzed. The administration, however, of muscarine, which stimulates the terminals of the pneumogastric nerve, will slow the pulse. showing that these are intact. It is evident, therefore, that the nicotine has paralyzed some peripheral portion of the cardio-inhibitory mechanism, which is not the nerve terminals. Since the stimulation of the venous sinus in the frog will also arrest the heart, the action is presumably upon the sympathetic ganglion which is located on the vagus.

As a result of the introduction of nicotine into the circulation there is a brief primary stage of increased secretion. In the salivary gland this occurs after section of the chorda tympani nerve, if the nerve is divided centrally to the superior cervical ganglion, but not if it has been cut between the ganglion and the gland. The primary stimulation is followed by a cessation of secretion. During this second stage electric irritation of the chorda tympani nerve above the superior cervical ganglion is no longer able to call forth secretion as it normally does, but pilocarpine will lead to an increased secretion.

The peristaltic movements of the intestines, after a transient in-

hibition, become much more active than normal, and there is also frequently an increase in the muscle tonus. According to Magnus, this stimulant action is due to an effect on Auerbach's plexus.

LOBELIA.

Materia Medica.—The leaves and tops of the *Lobelia inflata,* an herbaceous annual found throughout the eastern portion of the United States, producing pale or yellowish-green flowers in racemes. The dried plant has a slight irritating odor and a taste at first scarcely perceptible, afterwards burning, acrid, and attended by a flow of saliva. Proctor discovered the alkaloid *lobeline,* which was long believed to be liquid, until J. U. and G. G. Lloyd obtained it in broad, colorless, odorless, and tasteless crystals.

Official Preparations:

Fluidextractum Lobeliæ .....1 to 5 minims (0.06–0.30 mil).
Tinctura Lobeliæ (as an emetic 1 fluidrachm, 4 mils) .....20 minims (1.3 mils).

Physiological Action.—Lobeline has two characteristic effects, first of which is a curara-like action upon the peripheral ends of the motor nerve and the other a nicotine-like action upon the sympathetic ganglia. There is also some evidence of a primary stimulation of the medulla.

Respiration.—The moderate dose of lobeline is followed by a transient but well-marked increase in the rate of the respiration. This is probably due to a stimulation of the respiratory center, although the drug appears to have a marked action upon the pulmonary branch of the pneumogastric. Both Dreser, and Dixon and Brodie find that the drug produces a relaxation of the bronchial muscles. According to the latter investigators, however, this effect is preceded by a short stage of constriction, and is much more marked if the bronchi have been narrowed previously by a bronchial-contracting poison as pilocarpine.

Circulation.—Following the injection of lobeline into a vein, there occurs at first a marked slowing of the pulse with fall of the blood-pressure, followed in a few seconds by a rise in the pressure and an acceleration of the pulse beyond the normal. If the dose be not too large the pressure then gradually returns to the norm, or perhaps a little below. The first slowing of the pulse appears to be due in part to a stimulant action upon the inhibitory center in the medulla, but chiefly to an action upon the peripheral inhibitory ganglion. The fall of pressure is probably the result merely of the extreme slowing of the pulse.

The rise of pressure which follows the transient fall is caused partly by the increase in pulse-rate, but chiefly by the constriction of the blood-vessels. This narrowing of the vessels is not prevented

by section of the cord, and represents a primary stimulation of the vasomotor ganglia of the sympathetic system. According to Edmunds, there is, following this primary stimulation, a widening of the blood-vessels.

While the changes in the pulse-rate are largely the result of an action on the cardio-inhibitory ganglia, Edmunds found that neither muscarine nor pilocarpine would arrest the heart after a large dose of lobeline, and that if the heart had been stopped with muscarine lobeline would cause it to commence beating again, although at a slower rate than normal. These phenomena he believed to indicate that the lobeline acted in some way directly upon the heart muscle.

Secretion.—The effects of lobeline upon the secretion are precisely the same as those of nicotine; namely, a primary increase followed by a secondary cessation, both effects being the result of an action upon the sympathetic ganglion.

In the cat lobeline produces a primary dilatation of the pupil, followed by contraction; these effects do not occur when the drug is instilled directly into the eye. The first dilatation seems to be due to a stimulation of the sympathetic ganglion, but the secondary contraction must be due not only to a sequent paralysis but also to some stimulant action upon the oculomotor nerve, since it occurs in animals in which the superior cervical ganglion has been extirpated.

The vomiting which is caused by lobeline seems to be due in part to the local irritant effect, but also in part to a stimulation of the vomiting center in the medulla.

Therapeutics.—As an emetic lobelia is no longer employed, as we have other agents much safer. The only practical use of the drug in medicine is in the treatment of bronchitic asthma. In this condition, by virtue of its emetic properties, it tends to establish bronchial secretion, as do the nauseating expectorants, and, because of its action upon the pulmonary branch of the pneumogastric, to relax the spasm.

GELSEMIUM.

Materia Medica.—The rhizome and root of *Gelsemium sempervirens,* the yellow or Carolina jessamine, a beautiful climbing plant of the Atlantic Southern United States, distinguished by its large, axillary, very fragrant, clustered blossoms and perennial dark-green leaves. According to Cushny, gelsemium depends for its activity chiefly upon gelseminine,* the alkaloid gelsemine which was discovered by Wormley being comparatively feeble in its action. The root is a yellowish color, and light and fibrous.

Official Preparations:

Fluidextractum Gelsemii .....3 to 5 minims (0.2–0.3 mil).
Tinctura Gelsemii (10 per cent.).....15 to 30 minims (1–2 mils).

* Sayre asserts that the substance known as gelseminine is a mixture of two substances, for which he suggests the name gelsemoidine and gelseminine.

Physiological Action.—The alkaloids gelsemine and gelseminine differ markedly in their physiological effects. Gelsemine is primarily a stimulant to the motor cord and in large doses a paralyzant to the peripheral ends of the motor nerves. Gelseminine, which is much more toxic, appears, on the other hand, in no dose to act as a spinal stimulant, but causes in both the frog and the rabbit, according to Cushny, a gradually increasing paralysis by a depressant action upon the motor ganglia of the spinal cord. After very large doses this alkaloid also depresses the peripheral motor nerves.

Respiration.—Gelsemium usually kills by a paralysis of respiration. According to the researches of Burdon Sanderson and of Ringer and Murrell, immediately after the ingestion the extent of the respiration, but not its rate, is increased; very shortly, however, both rate and depth enter a condition of progressive palsy, ending in death. The respiratory changes are the product of a direct action upon the respiratory centers, being uninfluenced by previous section of the vagi.

Circulation.—The action of moderate doses of gelsemium upon the circulation is not pronounced, but the toxic dose depresses both the pulse-rate and the pressure. As this occurs after previous section of all the cardiac nerves and the spinal cord, it is probable that the poison exerts a direct influence upon the heart. How far or in what way it affects the arterial system we have no knowledge.

Eye.—Ringer and Murrell affirm that decided, non-toxic, doses of the drug cause contraction of the pupil. However this may be, marked dilatation of the pupil is a very constant symptom in the poisoning, and the local application of gelsemine to the eye produces violent mydriasis, with paralysis of accommodation, probably through an action on the ends of the oculomotor nerves.

Toxicology.—The symptoms of gelsemium poisoning are, first, a feeling of languor with dizziness, frontal headache, and usually disturbance of vision; later, profound muscular weakness with staggering gait, if the patient be able to walk, dropping of the jaw, ptosis of the eyelids, diplopia, pupil dilated, respiration slow and labored, pulse feeble and thready, skin cold and wet. Consciousness may be preserved until very late in the poisoning, but frequently there is considerable drowsiness. The drug acts promptly, symptoms appearing within twenty minutes beginning to subside within two or three hours. The treatment should be conducted on general principles, Lugol's solution as a chemical antidote and the rational use of such stimulants as strychnine.

Therapeutics.—Gelsemium was originally employed as an arterial sedative and febrifuge in the malarial fevers of the South, and subsequently in other sthenic fevers. It appears in some way to depress the bodily temperature, but it does not appear probable that any advantage to be derived from it will counterbalance the danger attending its employment in the large doses required. In asthma, spasmodic

laryngitis, whooping-cough, and nervous cough it has been recommended by Bartholow, but is little used. The testimony to its value in cases of trigeminal, ovarian, and other neuralgias is strong. How it does good in these disorders is as obscure as is the nature of the neuralgias, and in our hands it has usually failed. The marked effect of the drug upon the facial nerves would appear to indicate its employment in facial neuralgias, and especially in facial spasmodic affections.

LOBELIA.

Dixon and Brodie.....J.P., 1903, xxix.
Dreser .....A.E.P.P., 1889, xxxvi, 237.
Edmunds .....A.J.P., 1904, p. 80.
Muto and Iwakawa.....A.E.P.P., 1910, lxii.

GELSEMINE.

Cushny .....A.E.P.P., xxxi, 49.
Ott .....P.M.T., vii, 289.
Ringer and Murrell.....L.L., 1876, i, 83.

CONIUM.

Hayashi and Muto .....A.E.P.P., 1901, xlviii, 356.
Kolliker.....V.A.P.A., x, 228.

NICOTINE.

Langley and Anderson.....J.P., xxvii, 224.
Langley and Dickinson.....J.P., 1890, xi, 265.

DRUGS USED TO PARALYZE PERIPHERAL SENSORY NERVES.

There are a considerable number of agents which have the power of destroying more or less completely the function of the peripheral endings of the sensory nerves, in some cases the paralysis being preceded by a stage of excitation. Many of these substances, although useful as local anæsthetics, possess other therapeutic virtues of greater importance, and have, therefore, been considered elsewhere in this work. Among these may be mentioned phenol, menthol, quinine, and aconite. In this chapter will be considered cocaine and its allies.

COCA.

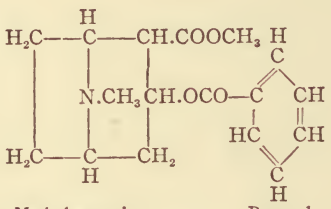
Materia Medica.—As far back as we have any historical record the cultivation of coca was an established industry in South America. Among the ancient Incas the plant seems to have been considered semi-sacred and to have been used in many of their religious rites. There are at least two species which are commercially the sources of coca; namely, the *Erythroxylon coca,* known as Huanuco or Bolivian coca, and the *E. truxillense,* Truxillo or Peruvian coca. These are shrub-like trees, 6 to 12 feet in height, which are found along the eastern slope of the Andes Mountains, from 1500 to 6000 feet above the sea.

The annual output is estimated at eighty million pounds, most of which is consumed in South America.

Coca leaves are one to two inches in length, elliptical or oval in shape, not dentate, and are distinguished from other medicinal leaves by a slightly curved line, running from the base to the apex, on each side of the midrib, and produced by the peculiar folding of the leaf in the bud.

Their odor, especially of the Truxillo variety, resembles that of tea leaves; the taste is bitterish and leaves a peculiar numbness of the mouth and lips. Coca depends for its activity on the presence of *cocaine,* of which alkaloid it contains about one-half of one per cent. Cocaine occurs in colorless, transparent prisms, soluble in six hundred parts of water, and forms with the acids bitter, soluble, crystallizable salts. It may be decomposed by various measures into methyl alcohol, benzoic acid, and a substance known as ecgonine. Besides cocaine, the leaves contain a peculiar tannin, known as *coca-tannic acid.*

Cocaine is benzoyl-methyl-ecgonine, which is proven not only by the products of its decomposition but also by its synthesis from these radicals. Its structural formula is:



Cocaine.

Ecgonine is allied to tropine in its chemical structure—differing only in that a hydrogen atom of tropine is replaced, in the ecgonine, by a carboxyl group—and cocaine, in many of its physiological actions, especially on the central nervous system, resembles atropine.

Coca leaf contains, besides cocaine, small quantities of several other alkaloids of similar composition and action, and probably also some free ecgonine.

Official Preparations:

Cocaina .....¼ to ½ grain (0.016–0.03 Gm.).
Cocainæ Hydrochloridum .....¼ to ½ grain (0.016–0.03 Gm.).

Physiological Action.—*Local Effects.*—Locally cocaine not only paralyzes the peripheral sensory apparatus but also, probably by virtue of its ecgonine nucleus, stimulates the walls of the blood-vessels, so that the topical application of the drug produces, besides local anæsthesia, a blanching of the part. While the action of cocaine is most

powerful upon the comparatively specialized end structure of the sensory nerves—including those of the special senses—it possesses also the capability of paralyzing the afferent nerve-trunks when brought in contact with them. Advantage is taken of this fact when producing the so-called regional anæsthesia.

The aqueous solution of cocaine is incapable of penetrating the unbroken skin, so that the local application over the external surface of the body does not produce anæsthesia. It passes through mucous membranes with a degree of readiness which is proportional to the thickness of the mucous membranes, and complete local anæsthesia may be produced, at least on comparatively delicate membranes, such as those of the eye or nose, by painting with a solution of the alkaloid. Some of the thicker mucous membranes, such as that of the urethra, however, are so resistant to the passage of the drug that it is very difficult to produce complete anæsthesia with it.

Circulation.—The action of cocaine upon the circulation is in some details not yet fully understood, but in the main our knowledge concerning it is clear. It produces a rise in pressure which is chiefly due to the stimulation of the vasomotor center in the medulla, although there is some evidence that the heart is also stimulated. The vasomotor spasm as shown by the blanching of mucous membranes after its topical application is probably a purely local action. There is no convincing evidence that when given internally it has any direct action upon the arterial muscles. Concerning the pulse-rate, there is much divergence of statement. According to Reichert, a very small dose of cocaine decreases the rate by stimulation of the cardio-inhibitory center, moderate doses increase the rate by depressing these centers and in some cases also the intrinsic inhibitory mechanism, while large doses may finally slow the heart by the action upon the motor ganglia.

Central Nervous System.—As stated above, ecgonine, in its effects upon the central nervous system, is allied to atropine. The ingestion of cocaine in sufficient quantities excites the brain, producing a condition of delirium similar in kind, although generally less marked in degree, to that produced by atropine. Small doses of the alkaloid, however, exercise a true stimulant effect on the intellectual functions, so that, like caffeine, it increases cerebration and tends to produce wakefulness.

Cocaine also excites the reflex centers in the spinal cord, producing, in the lower animals at least, spinal convulsions. Convulsions are also seen in cases of cocaine poisoning in the higher mammals and in man, but these convulsions are due, at least in part, to its effects upon the brain, since it stimulates in the cerebrum the motor areas as well as the psychical.

Muscles.—Upon the voluntary muscles cocaine exercises a direct action, in moderate quantities increasing their functional capacity, but in large doses paralyzing. In ergographic experiments upon man it

has been found that cocaine increases not only the muscular energy but also the resistance to fatigue. How far these results are due to a direct action upon the muscle substances and how far they are brought about through its stimulant influence upon the central nervous system is at present uncertain. Remarkable tales have been told of the effects of the coca leaf upon the South American Indians. Mixed with ashes, or a little lime, these leaves are chewed, and it is stated on reliable authority that so greatly does their use increase muscular strength and endurance that the natives are able to perform prolonged muscular exertion, going for twenty-four hours without food and without fatigue, although at the end of this period they will eat as much in a single meal as they ordinarily would consume in the whole day. Trials of the alkaloid cocaine as a preventer of fatigue have been made on several occasions on Europeans, but the results have not duplicated those just described. Whether the difference in effects is dependent upon the difference in constitution between the Caucasian and the Indian, or whether it is due, as claimed by many authorities, to the existence of other stimulant bodies in fresh coca leaves, is at present uncertain.

Respiration.—Small doses of cocaine increase distinctly the rapidity of the respiration, and in some cases also the depth. After toxic doses the respirations become at first rapid and more shallow, then irregular with interruptions, after each of which the respiratory movements begin deep and slow, but become more rapid and shallow until final arrest. As Mosso found that after section of the vagi cocaine causes an enormous increase of the rapidity of the breathing and at the same time so modifies the rhythm that expiration is no longer quicker than inspiration, it must be considered that the drug acts directly upon the respiratory nerve-centers as a respiratory stimulant. The first stimulant effect of cocaine upon the respiratory centers appears to be followed after fatal doses by a paralyzing influence which leads to death from asphyxia.

Intestines.—According to Von Anrep, the intestinal peristalsis is markedly increased by moderate doses. After large doses this increase is followed by great sluggishness, deepening into paralysis.

Eye.—When locally applied about the eye cocaine produces a dilatation of the pupil which, from a four per cent. solution, reaches its maximum in about an hour and disappears in from twelve to twenty-four hours. The dilated pupil is to some extent responsive to light and accommodation and can be further dilated by atropine or contracted by physostigmine.

The dilatation of the pupil by cocaine is due chiefly, if not solely, to a stimulant effect upon the peripheral ends of the sympathetic nerves, as is shown by the following facts: First, stimulation of the oculomotor nerve causes a contraction of the pupil; second, if the superior cervical ganglion is extirpated and a sufficient time for degeneration of the peripheral filaments allowed to elapse, cocaine will not

lead to widening of the pupil.* Since the ciliary muscles are supplied from the oculomotor nerve, the instillation of cocaine, at least in ordinary strengths, does not paralyze accommodation.

Temperature.—After poisonous doses of cocaine a marked rise of the bodily temperature has been observed, in some cases amounting to as much as 8 degrees F. Whether this effect is due to a direct action upon the thermogenic center or whether it is brought about by the increased muscular activity is not yet definitely settled, but the present evidence points toward a direct action on the heat-regulating mechanism.

Therapeutic Uses.—Cocaine is used: (1) As a local anæsthetic; (2) as a local vasoconstrictor; (3) to dilate the pupil; (4) as a respiratory stimulant; (5) as a circulatory stimulant; (6) as a general tonic, although its use for this latter purpose is hardly justifiable.

As a local anæsthetic cocaine is used chiefly in surgical work. There are four methods of applying it for production of surgical anæsthesia, the choice between which will vary according to the area and character of the operation. In operations around the eye, nose, and mouth, sufficient anæsthesia can usually be produced simply by applying a solution of cocaine over the mucous membrane. Strengths varying from two to ten per cent. may be employed, according to the degree of anæsthesia desired and the thickness of the mucous membrane. The cocaine must be allowed to remain in contact with the mucous membrane for a period of ordinarily about five minutes; the anæsthesia lasts about twenty minutes. In minor operations in which skin areas are involved a certain degree of local anæsthesia can be produced simply by injecting the cocaine beneath the skin in the neighborhood of the site of the operation. The anæsthesia produced by this method, however, is not always perfect and is of comparatively short duration, because the drug is absorbed so rapidly and carried into the general system. In portions of the body where it is possible to restrict the circulation, as in the extremities, perfect anæsthesia of indefinitely long duration may be produced by shutting off the circulation, as, for example, with a tourniquet, and then injecting cocaine into the neighborhood of the nerve-trunks.

As a vasoconstrictor cocaine is used in both acute and chronic congestions and inflammations, especially of the mucous membranes of the eye and nose. How far this method of treatment is of curative value in true inflammations is doubtful, but in congestions, especially

* This latter statement, however, is combated by Schultz, who asserts that after degeneration of the sympathetic nerve-endings, although the ordinary solutions of cocaine do not widen the pupil, if the alkaloid is applied sufficiently strong more or less dilatation will occur. If Schultz's observations are correct, then we must consider that strong solutions of cocaine have either a paralytic action on the oculomotor mechanism or else are directly stimulant to the radiating muscles of the iris.

of the mucous membrane of the nose, such as in acute coryza or hay fever, its local application gives at least temporary symptomatic relief. In chronic conditions, however, as hay fever, the remedy must be used very cautiously because of the danger of the formation of the habit. Cocaine is also used to constrict the blood-vessels for the purpose of checking local hemorrhage. As a vasoconstrictor cocaine has been largely superseded by the preparations of the suprarenal gland.

As a stimulant to the respiratory center cocaine ranks in its reliability probably next after strychnine, and is one of our most valuable remedies in the treatment of various narcotic poisonings. As a general circulatory stimulant it is not widely used, but may be of value as an adjuvant.

For whatever purpose a physician is employing cocaine, he should never forget the danger of the formation of cocaine habit. As a habit-forming drug cocaine is peculiarly seductive, because it increases the functional power of both muscles and intellect, augmenting not merely the capacity for useful work, but also for pleasure. Moreover, the habit is not only easily formed, but, once acquired, very difficult of eradication.

Toxicology.—There are two distinct types of cocaine poisoning, one occurring from the absorption of relatively large doses and the other occurring in persons who have an idiosyncrasy towards the drug, and generally from comparatively small amounts used for therapeutic purposes. In the first group of cases the symptoms are those of cerebral and motor stimulation: rapidity and confusion of ideation, sometimes marked delirium, exaggerated reflexes, epileptiform convulsions, generally not violent, pulse usually rapid and respiration hurried. The treatment is purely symptomatic, the outlook generally favorable.

In certain persons remarkably small doses of cocaine will cause alarming syncope; the patient becomes pale, pulseless, the respirations extremely shallow and far between, and there is usually more or less complete unconsciousness. The treatment of this condition is the same as that of any other syncopal state: the patient should be immediately placed in a horizontal position with the feet elevated, and rapidly-acting stimulants, as ammonia, strychnine, and camphor, administered hypodermically.

BETAEUCAINE.

The greater safety, as well as convenience, of the local over the general anæsthetics has led to a wide use of different forms of local anæsthesia by surgeons. Cocaine has certain obvious disadvantages which have limited its employment for this purpose; among these the most important are its relative toxicity, its local vasoconstrictor action, its effect upon the pupil, and the fact that many persons show a peculiar susceptibility towards it. In the effort to pre-

pare a substitute for cocaine which should possess its local anæsthetic powers but be free from its drawbacks, synthetic chemists have introduced a large number of compounds. It is to be noted that all of these contain the benzoyl nucleus and an aliphatic radical, generally methyl, combined with some ammonia derivative. While the efforts to obtain a cocaine substitute have been successful in so far as a diminution in toxic properties is concerned, yet it must be confessed that nearly all of them are anæsthetically inferior to cocaine; even much stronger solutions applied over mucous membranes will not produce the same absolute loss of all sensation that does the natural alkaloid. Of the long list of synthetic substitutes for cocaine, one, betaeucaine, has received official recognition, while several others are sufficiently employed to deserve a word of mention.

There have been two synthetic compounds introduced under the name of eucaine. In order to distinguish between them, these were known as alpha and beta eucaine. The former, however, has entirely disappeared from the market, so that the term eucaine is synonymous with betaeucaine. This is a trimethyl-benzoxy-piperidine. The hydrochloride of this base is recognized by the U. S. Pharmacopœia and occurs as odorless, crystalline powder, soluble in 30 parts of water and 35 of alcohol. The lactate is also upon the market, but is not official. It has the advantage over the hydrochloride of being more freely soluble.

Betaeucaine is not used for its systemic effect, but is occasionally administered by mouth for its anæsthetic effect upon the stomach, in doses of ½ to 1 grain (0.03 to 0.06 Gm.).

Betaeucaine differs from cocaine in that it does not possess the stimulating properties of the latter alkaloid upon the central nervous system and circulation; that it does not dilate the pupil, and is not a local vasoconstrictor. It is one of the least poisonous of the cocaine substitutes, its toxicity being estimated at from one-fourth to one-sixth of that of cocaine. While as a local anæsthetic in solutions of the same strength it is weaker than cocaine, yet because of its slight toxicity there is much less danger of poisoning from its use. It may be employed in strengths of from 1 to 5 per cent., according to the purpose for which it is applied. In order to prolong the anæsthetic action, especially over mucous membranes, it is frequently combined with epinephrin; the latter agent, by causing violent constriction of the blood-vessels, prevents the carrying away of the drug by the circulation and appears also to enhance the anæsthetic power.

Tropococaine.—This alkaloid is found in small quantities naturally in the coca leaf, but the bulk of the commercial supply is obtained synthetically. Chemically it is a benzoyl-methyl-pseudotropein. In its general physiological action it resembles cocaine in that it is stimulant to the nerve-centers. It does not, however, cause local ischæmia, is only feebly mydriatic, and is about one-half as toxic as cocaine. It is used but little except in so-called spinal anæsthesia.

Stovaine.—Stovaine is the hydrochloride of benzoyl-ethyl-dimethyl-

amino-propanol. Weight for weight it is stated to be a more powerful anæsthetic than cocaine, and is also somewhat less toxic. It appears, however, to be a local irritant, and although it is widely employed for the production of spinal anæsthesia, it is probably inferior to other remedies of this class.

Novocaine.—The hydrochloride of para-amino-benzoyl-diethyl-amino-ethanol occurs as colorless, crystalline needles soluble in their own weight of water. It appears to be the least toxic of all the cocaine substitutes, with the exception of eucaine. Its local anæsthetic action, while approximately equal to that of cocaine, is more transient. When locally applied it has no effect upon the blood-vessels or upon the pupil. It may be sterilized by boiling.

Orthoform.—The compound originally introduced under this name has been withdrawn from the market in favor of a very closely allied synthetic, the meta-amino-para-oxybenzoate of methyl, which, in order to distinguish it from the older form, is sometimes spoken of as "orthoform new." It occurs as a bulky white crystalline powder, almost insoluble in water, but forming a hydrochloride which is fairly soluble. Because of its relative insolubility orthoform is not an efficient anæsthetic, either for hypodermic use or when applied to mucous membranes, but has a marked effect when applied to raw surfaces. In painful conditions of the stomach relief by orthoform is by some considered an evidence of ulceration. It appears to possess some antiseptic power as well as anæsthetic, and is used as a dusting powder to burns and to relieve pain in gastric ulcer and tuberculous laryngitis. In gastric ulcer from five to ten grains (0.3–0.6 Gm.) may be given at a dose.

Anæsthesin.—Three compounds closely allied to orthoform are known as anæsthesin, propæsin and cycloform, which are respectively the ethyl, propyl and isobutyl esters of amino-benzoic acid. They are each sparingly soluble in water, of relatively low toxicity and possess greater or less antiseptic powers. They are used to relieve the pain of open ulcers, especially after burns, in gastric ulcers, tuberculous laryngitis and similar conditions. They seem to differ from orthoform in being able to penetrate mucous membranes, although because of their slight solubility their action through the unbroken mucosa is very slow. Externally they may be applied either as dusting powder or ointment in strengths of from five to ten per cent. In gastric ulcer from 1 to 5 grains (0.06–0.30 Gm.) may be given at a dose.

Holocaine.—This is a condensation product of acetphenetidin and paraphenetidin. It is marketed in the form of the hydrochloride, which is a neutral crystalline substance soluble in about 50 parts of water. In preparing solutions of it, porcelain vessels should be used, as at boiling temperatures the alkali of glass will decompose the salt and cause a precipitation of the free base.

While holocaine appears to exceed cocaine in anæsthetic power, it is also more toxic. In mammals it causes convulsions, probably of cere-

bral origin, and in larger quantities is a powerful muscle poison. The only apparent advantage it possesses is the fact that it is actively germicidal. It is used chiefly in ophthalmology in strengths of from one-half to one per cent.

SPINAL ANÆSTHESIA.

In 1898 Corning suggested the injection of a solution of cocaine into the subarachnoid space for the purpose of producing an anæsthesia in the lower extremities. The method, although for a time largely employed by a number of surgeons, was, because of the unpleasant symptoms and several fatalities, almost completely abandoned. The invention of the various substitutes for cocaine which were much less toxic led to a revival of the method, and it is at present employed by some enthusiasts almost to the exclusion of other methods of anæsthesia. Although, for reasons which I will mention later, it is highly improbable that this method will ever displace ether or chloroform, it seems to have certain advantages in selected cases.

Technique.—It is impossible to make a fair judgment concerning the anæsthetic of choice for this operation. Tropococaine, novocaine, stovaine, etc., each has its own advocates, all of whom claim that the unpleasant effects which others have reported from the method are due to the use of the wrong anæsthetic. The dose employed is ordinarily about three to seven centigrammes (one-half to one grain).

For the injection it is necessary that the utmost care be exercised in regard to asepsis. The needle, the solution, and the skin around the area of injection should be sterilized with the same thoroughness as for a major operation. The patient is seated and bent forward, so as to exaggerate the intravertebral spaces in the lumbar region, and a needle provided with a stylet inserted between the second and third lumbar vertebra, a little to one side of the median line. After the penetration of the ligamentum subflavum, which the surgeon learns to recognize by the sense of touch, the stylet is withdrawn and the needle pushed gently and slowly deeper until its entrance into the spinal canal is shown by the escape of cerebrospinal fluid. At least as much of this fluid should be allowed to escape as the volume of fluid to be injected; indeed, a number of authorities insist that the amount of spinal fluid withdrawn should always exceed the quantity of fluid injected. After the injection the patient should immediately be placed in the recumbent posture with the head slightly elevated. The anæsthesia begins within a few minutes and lasts generally from one to two hours. With some modification of the technic it is possible to produce anæsthesia as high as the upper part of the thorax, but, with the exception of a few whose enthusiasm has overcome their judgment, the method is rarely employed except for operations upon the lower extremities and the abdomen. Under ordinary cir-

cumstances the anæsthesia usually extends upward to near the level of the diaphragm.

Comparative Value.—The obvious advantages of the method are that it does away with the necessity of an anæsthetist, the lack of direct influence upon the circulation or mucous membrane of the lungs, and perhaps a lesser tendency towards shock. These, however, are outweighed by the question of relative safety, both immediately and subsequently.

While the advocates of this method claim, as one of the arguments in its favor, that it is safer than the general anæsthetics, practical results do not substantiate this claim. McCardie has collected 24,000 cases with a mortality of one death in 826. His figures, however, are rejected by some because he is openly opposed to the method, but Straus, who may be regarded as one of its advocates, grants a mortality of one in 1800, based on a collection of 30,000 cases. Even accepting the statistics of Straus, we must place the mortality at approximately twice that for chloroform and more than eight times as high as that of ether. Moreover, there have not been lacking a number of very unpleasant symptoms and sequelæ. Meningitis of non-septic nature, and, therefore, apparently, fairly attributable to the anæsthetic, has been reported; frequent palsies, some of which have proved permanent, although generally complete recovery has occurred within a few weeks, have been the most serious of the non-fatal results. These palsies are to be attributed probably to changes either in the anterior horns of the gray matter of the cord, which have been demonstrated histologically by Wassidlo and Spiller, or to degeneration in the posterior root nerves, as noted by Leopold.

It seems evident that as a routine method for producing anæsthesia the spinal injection of local anæsthetics cannot compete with the use of ether. It probably has, however, a field of usefulness in selected cases where ether is contra-indicated. The most important of these is in conditions of feeble circulation.

A word may be spoken concerning the minor modifications of technic which have been suggested for the purpose of lessening the danger of the method. The sudden respiratory failures which have occurred shortly after the injection have been attributed by some to the anæsthesia diffusing too rapidly and reaching the medulla. Attempts have been made to localize it by combining it with adrenalin. Those who use adrenalin assert that their excellent results are due to this combination; those who do not claim that all the bad symptoms which have been reported from spinal anæsthesia are due to the adrenalin. Strychnine has also been suggested, apparently with the idea that by stimulating the medulla with the strychnine would lessen the danger of sudden collapse. The addition of strychnine to this solution is a highly irrational procedure, and experience, I think, has shown that it detracts from, rather than adds to, the safety of the method.

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CHAPTER IV.

CIRCULATION.

The maintenance of the intra-arterial pressure depends upon two antagonizing forces, the heart driving the blood forward, and the resistance to its passage offered by the blood-vessels. Work done by the heart may be varied, either by changing the number of contractions per minute, or by alterations in the force of each individual beat. The rate of the heart is determined: first, by the inherent rhythm of the cardiac muscle; and, secondly, by the influence of the central nerve system. This latter is exercised in two directions. There are the cardio-inhibitory mechanism, which tends to restrain the heart, and the cardio-accelerator mechanism, whose function it is to increase the rapidity of the heart. From a pharmacological standpoint, the latter is of comparatively little importance; there are almost no drugs of which it is definitely known that they stimulate the accelerator (augmentor) mechanism. For practical purposes we may say that drugs influence the rate of the heart almost solely through their influence upon some portion of the inhibitory apparatus. There are a few exceptions to this, for there is reason to believe that certain agents affect the cardiac rate by an action upon the heart muscle, but these exceptions are so few that the statement may be accepted almost as a generalization.

While, theoretically, slowing of the heart should reduce the amount of work done very greatly, yet, practically, we find that there is a degree of compensation between the rate of the heart-beats and the amount of blood pumped at each contraction, so that within reasonable limits the output of the heart remains nearly constant at various rhythms. Despite this compensation, however, if the reduction in the rate of the heart is very marked the amount of work done will be greatly diminished, and the blood-pressure consequently fall.

The methods in which drugs may change the blood-pressure may be conveniently arranged in a diagrammatic form as follows:

The following changes caused by drugs tend to elevate blood-pressure:

More work done by heart:
- Rate more rapid—
  - Inhibitory paralysis { central / peripheral
  - Accelerator stimulation.
- Greater vigor—
  - Stimulation of muscle or motor ganglia.

Blood-vessels constrict:
- Stimulation of vasomotor centers.
- Stimulation of arterial walls (peripheral).

The following changes tend to lower blood-pressure:

Less work done by heart:

Rate slower—

Inhibitory stimulation { peripheral / central

Muscular weakness.

Vigor of contraction less—

Depression of muscle or motor ganglia.

Blood-vessels dilate:

Paralysis of vasomotor centers.

Paralysis of arterial walls.

CARDIAC STIMULANTS.

The heart stimulants divide themselves naturally into two series: those which increase the tone of the heart—the so-called digitalis group—and those which merely excite it momentarily, including alcohol, camphor, and ammonia.

DIGITALIS GROUP.

The drugs which belong to the first of these series are so similar in their actions that they may conveniently be considered together, their individual differences being pointed out subsequently.

Physiological Action.—Probably all the members of the digitalis group are more or less irritant to mucous membranes. A number of them are quite actively so. Formerly the nausea as well as the diuresis which follows their exhibition was supposed to be due to local irritation of the gastric or renal mucosa respectively, but the work of Hatcher and Eggleston has demonstrated that these drugs have a direct action upon the vomiting center and there is strong reason to believe that the effects upon the kidney are chiefly due to circulatory changes caused. Nevertheless it is not improbable that local irritation may explain, in part at least, the differences in these regards between individual members of the series. Many of them are also possessed of considerable local anæsthetic power and one or two have even found a certain degree of clinical use for this purpose.

Probably all of the series are stimulating to the unstriped muscle fiber all over the body. Although the action is quite subordinate to the effects upon the circulatory muscles, it has been shown that the intestinal and uterine muscles are often markedly affected by certain members of this group.

Heart.—The most apparent effect of small doses—and by small I mean those which are ordinarily employed for therapeutic purposes—of digitalis is a reduction in the rapidity of the heart beat with some increase in the size of the pulse wave, and in man at least without any marked variation in the blood-pressure. If the dose be somewhat larger the pulse-rate becomes extremely slow, falling sometimes as low as 30 or 40 per minute, and the amplitude of the cardiac excursions very great, the blood-pressure usually being more or less elevated. At this stage, or a little later, various forms of irregularity in the rhythm

of the heart may develop. Whereas, in the first stage of digitalis action the retardation of the pulse is due solely to prolonged diastolic period; subsequently the duration of the systole is also augmented. Beyond

(Normal.) (Therapeutic stage.) (Toxic stage.)

FIG. 16.—The action of digitalis on the circulation. Note the slow full pulse with rise of pressure in the therapeutic stage, and the extremely rapid small pulse, due to incomplete diastole with sudden cessation of the heart, in the toxic stage. Time marker indicates 1 second.

this degree of action it is rarely possible to go in clinical use of the drug, because of the violence of the secondary manifestations produced by it, especially in the alimentary tract. The change produced by larger poisonous doses will be treated of later.

The effects produced on the normal circulation by doses of digitalis ordinarily employed for therapeutic purposes, I believe, are due entirely to a stimulant action upon the inhibitory mechanism with possibly some increase in the contractile power of the heart muscle. Contrary to the views formerly held almost universally, it now appears that the output of the heart in a given period of time is somewhat lessened at this stage of action. At least it is not increased; if it were we should expect the blood-pressure to be elevated, for as far as we know any dose of digitalis sufficient to affect the vasomotor mechanism tends towards vascular constriction. Moreover, there is evidence that in the early stages of digitalis action the diastole is more complete than normal, that is, there is a reduction in muscle tone precisely corresponding to that one would expect from stimulation of inhibitory mechanism. On the other hand, the size of the pulse wave seems somewhat larger than one would expect from a purely inhibitory action.

It is to be remembered that the effect of exciting inhibitory mechanism is not merely to reduce the rapidity of the heart contractions, but to diminish the tone of the muscle and its irritability. With strong inhibitory stimulation there is delayed conduction through the muscle of the heart with sometimes a blocking of the impulse either at the sino-auricular or the auriculo-ventricular juncture. Under digitalis, to a certain extent, the loss of tone and irritability are overcome by the action of the drug upon the muscle of the heart, but not infrequently a partial heart block may be caused by digitalis, in most cases through its action upon the inhibitory mechanism, and the same thing is probably true of sinus arrhythmia.

Probably the second earliest change to occur is increase in the contractile power of the heart with consequently more powerful systole and greater output of blood. Later there is also an increase in tonus and a correspondingly imperfect diastole. Probably later than both of these changes is the increase in irritability in the muscle. This leads at first to the appearance of extra systoles—sometimes spoken of as abortive diastoles—because the relaxation of the heart is interrupted before completion, by the impulse to contract. Often these extra systoles occur at regular intervals, giving a coupled rhythm; that is, two impulses following closely and then a longer period of rest, this doubling of the pulse recurring at regular intervals. This type of pulse is also known as the *pulsus bigeminus,* or sometimes incorrectly as a dicrotic pulse.

Later the increase in muscular irritability becomes so great that the heart entirely escapes from the control of the vagus and the pulse-rate becomes extremely rapid. This change, which is a late toxic manifestation, generally takes place rather suddenly.

We may therefore sum up the changes in the activity of the heart

which are induced by digitalis as follows: slowing of its rate, due to inhibitory stimulation; increase of contractility and increase of tone brought about by direct action upon the muscle; a delay of conduction probably through the action upon the vagus, although under certain circumstances it appears to be of muscular origin; and increase of irritability of the muscle. In the normal heart the last two are seen only after poisonous doses, but in certain diseased conditions quantities within the therapeutic limit sometimes produce them.

The question of the comparative influence of these drugs on the various chambers of the heart is one of much practical importance,

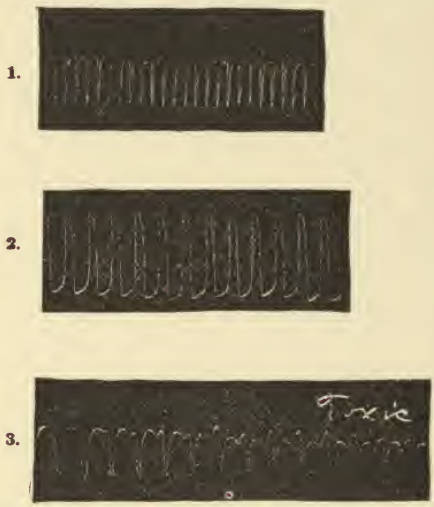

FIG. 17.—Showing the action of strophanthin on the frog's heart. 1. Normal. 2. Therapeutic stage. 3. Toxic effects.

but one concerning which our information is not conclusive. In the frog the auricles may often be seen widely distended with blood and vainly making efforts to empty themselves at a time when the ventricle is firmly contracted in systolic spasm. Moreover, the experiments of several investigators have shown that the rise of pressure is much less in the pulmonary artery than in the systemic arteries. It seems evident, therefore, that the greatest action of these drugs is upon the left ventricle. It is certain, however, that there is an increase in the force of the right ventricle and probably also some stimulation of the auricle. It would naturally be expected that the effect upon the left ventricle would be greater than upon any other portion of the heart on account of the greater amount of muscular tissue, but whether or not the action upon the various chambers of the heart is, as is sometimes affirmed, in direct proportion to the amount of their muscle tissue is uncertain. All that we can say is that all the chambers of the heart are probably stimulated, but the left ventricle more so than any other.

Vasomotor Mechanism.—The rise in blood-pressure which follows the injection of digitalis in the lower animals, with almost certain regularity, is due, at least in large part, to a contraction of the blood-vessels. This may be shown not only plethysmographically, but also by measurement of the velocity of the blood current. After full doses, at least, the resistance of the blood-vessels may be so increased that, despite the greater activity of the heart, the rate of flow through the arteries is slower than normal. Contrary to the statements sometimes made, this vasomotor action is common to all members of the digitalis group, although not equally well marked in all.

In somewhat startling contrast to the long known effects of digitalis in the lower animals are the recent studies of its effect upon blood-pressure in human beings. Practically all investigators of this point are agreed that as used clinically digitalis generally does not produce an increase of arterial tension. The discrepancy between the conclusions of the pharmacologist and the clinician is probably due to differences of dosage. Joseph, from perfusion experiments, reaches the conclusion that digitalis exercises a double influence upon blood-vessels, a transient primary dilatation, and a secondary contraction, much more permanent. He noted that when the dose was very small the action upon the vessels was predominantly relaxing, but that after large quantities even primary dilatation might be absent, the vascular effect being constrictor.

It is important to note that the effect upon different vascular areas is not the same. The constricting action is most marked in the splanchnic area, and least so in the kidney. In many cases there is an absolute dilatation of the renal artery, but even when this does not occur there is a relative dilatation; in other words, the renal artery being less markedly contracted than the abdominal organs, the tendency is for a disproportionate amount of blood to be forced through the kidneys.

The effects of the digitalis series may be greatly modified by the existence of circulatory or systemic diseases. In infectious fevers not only may digitalis fail to slow the pulse but its effect upon the vasomotor mechanism and the cardiac muscle is often very much less powerful than in normal individuals. It is probable that the failure of digitalis to raise the blood-pressure is, in many cases, due to degenerative processes in the circulatory muscle, for Meyer has found that in the advanced stages of poisoning by diphtheria toxin none of the circulatory stimulants with which he experimented were capable of producing any pronounced rise in the blood-pressure.

In cases in which the heart muscle is diseased, not only may the characteristic actions of digitalis be lacking, but the drug may produce effects not seen in the normal animal. These discrepancies will be discussed under the therapeutic uses of the drug.

Kidneys.—As has already been pointed out, the renal blood-vessels are less powerfully constricted than the other arteries; indeed, often they are actually widened. The result of this relative or actual dilata-

tion of the vessels of the kidney means an abnormal amount of blood passing through them, which will tend to increase the quantity of urine secreted. Whether the diuresis is the result of this increased flow of blood, or whether the local widening of the vessels is due to the greater functional activity of the kidney, the result of a direct stimulant influence upon the renal epithelium, is as yet unsettled. The widespread belief among clinicians that these drugs are injurious in cases of nephritis indicates that their diuretic power is due to their local stimulating action upon the kidney, and that the circulatory changes are secondary.

Therapeutic Uses.—While the greatest use of the digitalis group is in chronic conditions they are often valuable stimulants in the treatment of acute circulatory failure occurring either in the course of adynamic fevers, as the later stages of pneumonia, or as a result of acute poisoning, or of nervous origin, such as surgical shock. As already pointed out, however, they often fail to act in febrile cases. In conditions of great urgency, such as surgical shock, it is useless to give them by the mouth because they are so slowly absorbed. Some preparation, as strophanthin, which is suitable for intravenous injection, should be chosen under such conditions.

A number of eminent physicians have asserted that they have obtained excellent results in the treatment of delirium tremens with large doses of digitalis. The evidence of the value of the remedy in such cases is too strong to be overlooked, but this does not indicate the possession of any narcotic properties by the drug. The rest and sleep which have followed its administration have probably been the result of the increased flow of blood to the nerve-centers. Enormous doses of the drug are tolerated in these cases, although their use is not entirely free from danger.

The most important uses of digitalis are in various types of chronic cardiac insufficiency. It must be borne in mind that in these conditions there are often irreparable lesions in the heart, and we cannot therefore hope to cure the patient in the sense of restoring conditions to the normal. No useful purpose is served—except in certain extreme states—in attempting to merely excite the heart to greater activity unless we can upbuild its functional power so that it shall be able to carry out the task of maintaining the circulation despite the obstacles due to its diseased condition.

There are only two measures which tend to restoration of power in an exhausted organ—and the heart with broken compensation is practically exhausted—these are rest and food. We should, therefore, strive to lengthen the period of cardiac rest as much as possible without destroying the efficiency of the circulation, and to provide as abundant nutriment as circumstances will permit.

As the cardiac diastole is the only period of functional rest for the heart, slowing of the pulse has a favorable influence on the anabolic processes in that organ. It would, at first thought, seem that the

slowing would seriously diminish the work done by the heart and therefore interfere with the necessary circulation of blood through the body; but the diminution in the amount of blood pumped, because of the reduction in the cardiac rate, is much less than might be expected. It has been experimentally shown that there is a compensatory relation between the size of the pulse-wave and the rapidity of the heart's action. This is due to the fact that during the period of diastole blood is constantly flowing from the great veins through the auricle into the ventricle; the contraction of the auricle is but the active final finish to the passive filling of the ventricular cavity. As the blood is flowing into the ventricle constantly during the period of diastole, it follows that the longer the period of diastole the greater amount of blood which will be in the ventricle when it begins to contract, and, if it contract with normal completeness, the larger the pulse-wave. As the slowly-acting heart forwards the same quantity of blood with fewer contractions, it is evident that there is less muscular energy expended, and the slowly-acting heart, therefore, not only has greater time for recuperation, but is also acting more economically. The explanation of this apparent paradox rests in the fact that if the ventricular cavity is not completely filled with blood at the beginning of the contraction a considerable amount of energy is wasted in reducing the size of the cavity to correspond to its contents.

The nutritive supply to the heart is mainly through the coronary arteries. The location of these arteries—comparatively small vessels springing at right angles from a very large one—is unfavorable for their filling unless the pressure in the aorta be considerable. When a large volume of blood is thrown out into the aorta suddenly, as from a well-filled heart, because it cannot escape as rapidly from the aorta as it enters, there is a period of high pressure in the aorta, and consequently the coronary arteries are better filled by a big pulse-wave than by a small one. The slowing of the heart's action, therefore, not only gives it more rest but more nutrition.

For the purpose of systematic consideration we may divide the chronic heart diseases into three groups: simple muscle lesions without changes in the rhythm; valvular diseases, either with or without changes in the muscle but having normal rhythm; and arrhythmias, whether accompanied by valvular lesion or not.

Under the first group of cases, those of simple myocardial changes, may be included not only those in which there is degeneration of the muscle fibers, but also cases of simple dilatation, the result of undue strain beyond the reserve capacity of the heart. When there is actual protoplasmic alteration in the muscle fiber, digitalis will generally not prove of very great benefit. I cannot hold with those who teach that fatty degeneration of the heart is of itself a contra-indication to the use of digitalis, but it is evident that a muscle fiber whose protoplasm has been replaced by either fibrous or adipose tissue cannot contract under the influence of digitalis, any more than without the drug, and

that as far as the effect of digitalis upon the muscle tissue is concerned, it can exercise but little beneficial effect. On the other hand, if the pulse-rate be rapid, digitalis by slowing it places the heart in a position to accomplish its work with the greatest possible economy, and by increasing the functional power of what healthy muscle tissue is left may enable the heart to disembarrass itself of a temporary load and restore conditions more favorable for nutrition of the heart. The drug should under these circumstances be used cautiously, remembering that large doses predispose to some of the arrhythmias which are frequently the terminal stages of myocarditis. When there is simple dilatation without degeneration, digitalis often acts most happily. In these cases not only does the inhibitory stimulation and the better flow of blood through the coronary arteries encourage reconstructive processes, but if doses sufficiently large to increase the tone of the muscle be given, we are directly combating the essential lesion.

In valvular lesions there are certain mechanical factors which may modify seriously the value of digitalis; for instance, in aortic incompetency it is evident that the large volume of blood thrown out by the slowly-acting heart will, by increasing the pressure in the aorta, increase the regurgitation through the aortic valves. The slowing of the pulse in this lesion is not mechanically favorable to the work of the heart, and the inhibitory effects of digitalis are of no great benefit, but sometimes, by increasing the tone of the heart muscle, the drug may enable the ventricle to better withstand the dilating effect of the regurgitation and, therefore, be of service. In that rare condition, uncomplicated aortic stenosis, it is also manifest that the prolongation of diastole, which is the result of inhibitory stimulation, is of no special benefit. But on the other hand, the increase in ventricular power brought about by digitalis is of the greatest importance.

In diseases of the auriculoventricular valve the conditions are essentially very different; for, whereas in lesions of the aortic valve the greatest strain comes on the left ventricle, which is the strongest muscle of the heart, in mitral lesions the strain comes especially upon the relatively thin-walled auricle, or, if this fails, upon the right ventricle. In mitral obstruction the blood is unable to flow passively into the ventricle during the period of cardiac quiescence, and the auricle has too large a share of work to accomplish in filling the ventricle for its contraction. It is evidently of extreme importance in this condition to prolong the diastolic period in order to allow the great veins to empty themselves as completely as may be into the ventricle and thus lighten the burden of the auricle. The action of the digitalis group upon the auricular muscle is much less than upon the ventricular muscle, and the increase of ventricular tone may perhaps render it more difficult for the auricle to empty its contents. For these reasons aconite or veratrum often exercises a more beneficent effect than digitalis in cases of obstruction at the auriculoventricular valve.

In cases of mitral regurgitation the high intraventricular pressure caused by digitalis causes the blood to be driven backwards through the incompetent valve with greater violence; but since the element of friction will increase more rapidly at the narrow, tortuous orifice of the leaky mitral valve than at the larger opening into the aorta, although the regurgitant flow may be more violent, the proportion of blood which leaks backward may be diminished. If the muscle tone of the auricle be sufficient, the result of the action of digitalis will be mechanically favorable, because of the diminution in the proportion of leakage. On the other hand, where the left auricle is feeble the violence of the regurgitation may cause an acute dilatation of this chamber and thereby do much damage.

The cardiac arrhythmias may be divided into four groups: those due to irregularity of impulses sent out from the sinus node; those due to delayed conduction (heart block); those due to an excessive irritability of the ventricle (extra systoles); and those due to auricular fibrillation.

In the sinus arrhythmias there is no reason to expect that digitalis could do any good, beyond slightly improving the nutritional condition of the heart if there should be bad decompensation, and clinical experience has confirmed this deduction. In cases of heart block it is not only usually incapable of benefit but may prove highly injurious. If large doses be given, digitalis itself delays conductivity, and it is only fair to presume that even doses of the drug, which of themselves are too small to cause heart block, might sufficiently add to the already present resistance in the bundle of His, to completely obstruct the passage of impulses from the auricle to the ventricle. Moreover, it is probable that the excitation of the inhibitory mechanism makes the ventricle more refractory to the feeble impulses which may reach it. In cases of absolute heart block, however, it has been recommended in large doses with the idea that by increasing the rapidity of the ventricle due to the effect of heightening the muscle irritability, and by slowing the auricle through inhibitory stimulation, the two chambers of the heart will beat at a rhythm more nearly alike. It is, however, difficult to apprehend what real purpose this similarity in rate could serve, unless there was coördination of rhythm.

In the cases of extra systoles many advise against the use of digitalis on the ground that it increases muscle irritability and will itself cause this type of irregularity. It is to be remembered, however, that this excessive irritability of the heart follows only from large quantities of digitalis and smaller doses possess other properties which may be highly beneficial. The excessive irritability of the heart which is the cause of extra systole is an indication of poor nutrition in the cardiac muscle, and anything which tends to improve the nutritive state of the muscle will tend to correct this irregularity. This symptom is frequently the sign of beginning sclerotic change in the heart muscle, and it is often a constant fight to keep the heart equal to its task in order to preserve life and a fair degree of health. Personally, I am strongly of the opinion

that the use of small doses of digitalis in these cases is often of great benefit. The drug must be used carefully and one need not expect to see the brilliant dramatic improvements which are sometimes observed in other forms of heart disease, but I am convinced that I have not only prolonged life but made it more comfortable by the use of the drug.

A very considerable proportion of cases of chronic endocarditis eventually develop a condition, which is practically one of paralysis of the auricle, known as auricular-fibrillation. In this condition there is entire lack of coöperation between the muscle fibers of the auricle, so that instead of these contracting synchronously, and thereby expelling the blood, each muscle fiber contracts independently of its fellow, and the result is simply an inchoate useless movement of muscle cells. It is in these cases that are seen the most violent evidences of broken compensation, rapid and absolutely irregular pulse, anasarca and extreme dyspnœa. The most brilliant results which are produced by digitalis are in this type of case. The pulse, from a disorderly succession of rapid and almost impalpable waves may become in twenty-four or forty-eight hours a slow, regular and forcible beat. At the same time there is an equally rapid disappearance of the subjective symptoms and the profuse diuresis rapidly carries off the excess of intracellular fluid. To obtain good results in this condition it is essential that the drug be pushed to the full extent of the patient's tolerance. Fifteen or twenty minims of the tincture may be given three or four times a day until the pulse-rate is reduced to less than sixty, or the occurrence of nausea signalizes the saturation of the system. The mechanism by which digitalis produces this striking amelioration is as yet uncertain. It is not due simply to excessive stimulation of the vagus system, for even after paralysis of the terminals of this nerve by atropine digitalis will still slow the pulse and improve the patient's condition. The explanation most frequently offered is that by causing a block at the auriculoventricular junction digitalis prevents the succession of chaotic impulses arising in the auricle from passing over into the ventricle, and the latter therefore takes up its own rhythm and contracts slowly and regularly; but Cushny has pointed out that there is no convincing evidence that digitalis causes heart block except through its action on the inhibitory apparatus, and since the drug is efficacious after paralysis of inhibition he believes that some other explanation must be sought for. His own inclination is that by improving the circulation through the heart, and thereby the nutritive condition of the ventricular muscle, the drug reduces the irritability of the ventricle so that it is not so easily disorganized by the unregulated auricular impulses. While the most striking results are seen in cases of auricular fibrillation and while in a large proportion of them digitalis acts almost specifically, a considerable number of them are quite refractory to the drug. It is usually necessary in this, as in other chronic disorders of the heart, to continue the digitalis in order to maintain the benefit.

DIGITALIS.

Materia Medica.—Digitalis is the leaves of the *Digitalis purpurea,** or foxglove, a European perennial plant, largely cultivated for its beautiful purple, bell-like flowers. The leaves, which should be collected during the second year of the plant's growth at the commencement of flowering, are of a dull pale green with a whitish down underneath, from four to twelve inches in length, and have a bitter nauseous taste and faint narcotic odor.

Digitalis depends for its activity upon the presence of a number of glucosides, five being generally recognized as established, namely, digitoxin, digitophyllin, digitalein, and gitalin. These—as well as digitalin, which appears to be found only in the seed—act similarly upon the heart. There is also present in the leaves also a saponin-like body known as digitonin, which has none of the characteristic effects of the other principles. The term "digitalin" has been used with various meanings. The digitaline of the French Pharmacopœia appears to be identical with digitoxin. The "German digitalin" is not a pure principle, but a mixture consisting largely of digitoxin and containing true digitalin and digitoxin. The digitalin of Kiliani, which is found in the seeds, is often referred to as *digitalinum verum.* Of the various glucosides which have so far been examined, the most active is digitoxin, but while, from a quantitative point of view, this substance may be regarded as the most important active principle of digitalis, its effects are not the same as that of the whole leaf.

Official Preparations:

Digitalis	1 to 3 grains (0.06–0.20 Gm.).
Fluidextractum Digitalis	1 to 3 minims (0.06–0.20 mil).
Tinctura Digitalis (10 per cent.)	5 to 20 minims (0.3–1.3 mils).
Infusum Digitalis (1.5 per cent.)	1 to 4 fluidrachms (4–15 mils).

Physiological Action.—The general effects of digitalis have already been sufficiently described; it remains merely to point out in what regards it differs from the other members of the group. It is absorbed with much slowness from the intestinal tract, and the evidence of its action may be delayed for more than twenty-four hours. When, however, it once begins to manifest its presence it acts with great persistency. Because of its slowness of elimination it is peculiarly prone to give rise, when used over long periods of time, to those toxic manifestations known as the cumulative action (see page 185). It appears to be one of the most active vasoconstrictors of the group, but as pointed out previously this effect is brought about only by large doses. Its diuretic action is comparatively feeble; it rarely increases the flow of urine unless the patient be œdematous.

Therapeutics.—In pharmacological experiments digitalis itself has

* Probably all the species of digitalis have the therapeutic properties of *D. purpurea* to a greater or less degree, see H. Goldenberg (*Inaug. Diss.,* Dorpat, 1892), and it is probable that much of the digitalis on the market is derived from unofficial species.

not acted more powerfully than other members of the series, yet clinical experience has shown that in cardiac diseases it is by far the most certain drug of the group. For a detailed consideration of its use in chronic heart-disease see page 178.

Administration.—Various clinicians have expressed a great preference for one or the other preparations of digitalis, but, as a matter of fact, there is probably very little difference, if any, in the kind of action of the official preparations of the drug. The better results which have been obtained from one or the other have been due chiefly to the dose in which it has been administered; in other words, in equivalent quantities tincture and infusion are precisely parallel in their effects. Attention may be called, however, to the fact that a teaspoonful of the tincture is equivalent to about nine minims of the tincture.

Because of the variability in the potency of digitalis and of the desirability of a preparation fitted for hypodermic administration, there have been introduced a large number of preparations of digitalis and its principles. It is extremely doubtful whether any of these preparations possess any real advantage over the official ones. The old notion that the irritating and nauseating effects of digitalis could be separated from the cardiant action of the drug has been pretty thoroughly disproven. Any of the preparations of digitalis which are active are likely to nauseate if given in full doses by the mouth and will cause local inflammations if injected hypodermically. If, however, asepsis of the injection is perfect no suppuration will occur. The inflammatory reaction from the injection of some of these special preparations is probably less than that which would follow the hypodermic administration of a tincture of digitalis because of the local irritant action of the alcohol in the tincture, but at the same time it is certainly possible, as I have frequently done, to inject the tincture of digitalis into the subcutaneous tissue without any ill effects further than the temporary congestion and induration. But the use of digitalis hypodermically has been almost completely abandoned. As the nauseating effect is due to a central action it is manifest that the drug is as likely to upset the stomach when given hypodermically as when given by mouth, and if a prompt action is required much better results will be obtained by the intravenous administration of strophanthin (see page 187).

In using digitalis in conditions of any great seriousness the physician should be guided as to the quantity only by the effects. The different samples of the drug upon the market are so exceedingly variable in their potency that any statement as to the dose of digitalis can be only roughly approximated.

The skilful practitioner watches for the evidence of the action of digitalis not only in the improvement of the clinical symptoms, but also in certain toxic manifestations. The symptoms which indicate the therapeutic limit for digitalis are extreme slowing of the pulse, nausea or diarrhœa, and the occurrence of cardiac arrhythmias of a type not previously existing in the patient under treatment. If, on the occur-

rence of any of these symptoms the physician immediately stops the exhibition of the drug, there is no danger of any bad effects from its action, supposing that it has been indicated in the case at hand.

When the patient's condition is immediately threatening digitalis should be used boldly. In desperate situations as much as one or two fluidrachms of the tincture may be given at a single dose. After such heroic quantities no more of the drug should be exhibited the same day as it often requires 24 hours for the action of digitalis to be unfolded. In many cases of severe cardiac disease, when digitalis has been used freely, death has finally come by sudden syncope, while the patient was still going about and enjoying a comfortable life. We do not believe that the arrest of the cardiac action has been due to a direct action of the drug, but to the fact that the enormous doses have stimulated the heart and steadied its expenditure of force, so that it was enabled to go on until the last particle of cardiac vital power was exhausted.

When digitalis is administered persistently, its first evident influence may be suddenly developed after long delay. In cases of this so-called "cumulative action" the first symptom is usually a sudden drop of the pulse, which will be the most serious effect, provided that the administration of the remedy be at once suspended. It is a matter of much importance to determine when this cumulative action is to be expected. It is probably connected with slow absorption and elimination, and is much more prone to occur when there is no diuretic effect. It is also very likely to appear after tapping: the sudden removal of pressure from the vessels leads to the picking up from the tissues of serum—saturated, it may be, with digitalis principles—and also to the rapid absorption of any digitalis which may be in the alimentary canal.

It is also to be remembered that in cases in which the body temperature is very high the action of digitalis is much less marked than normal, and therefore, in pneumonia and other diseases which terminate with a sudden defervescence, some care should be exercised in the bold use of the remedy, else when the temperature suddenly falls inordinate digitalis effects may appear.

STROPHANTHUS.

Materia Medica.—Under the names of Kombé, Inèe, Onaye, and Pahouius poison, there have reached Europe various African arrow poisons, which are now known to be derived from one or more species of the tropical genus Strophanthus—apocynaceous climbing shrubs.

While many of the species of strophanthus, probably all of them, possess the characteristic influence over the circulation, the United States Pharmacopœia recognizes but one, the *Strophanthus kombé*. This is a woody vine, native to Africa, bearing yellowish, purple spotted flowers gathered into cymes. The official portion of the plant is the seeds, which are one-half to one inch in length, of a greenish-brown

color, downy, and characterized by a long awn. They depend for their activity upon the presence of a glucoside, *strophanthin,* of which they contain in the neighborhood of two per cent. This principle occurs as a white or faintly yellowish crystalline powder of an intensely bitter taste, freely soluble in water and in dilute alcohol, and sparingly soluble in absolute alcohol.

The term strophanthin has unfortunately been applied to several different substances. The *Strophanthus kombé* appears to contain two isomeric glucosides, one of which is crystalline and the other amorphous. The crystalline strophanthin has half the molecular weight of the amorphous variety and is between two and three times as active. Besides these there is in commerce a glucoside prepared from the *Strophanthus gratus* which is known as strophanthin-Thoms or as g-strophanthin. This appears to be identical with ouabain, the active principle of Acocanthera.

Official Preparations:

Tinctura Strophanthi (10 per cent.) .....3 to 6 minims (0.2–0.4 mil).
Strophanthinum .....$^1/_{200}$ grain (0.3 Milligm.).

Physiological Action.—*Local Action.*—Locally, strophanthus and strophanthin are exceedingly irritant to mucous membranes. Strophanthin is also somewhat anæsthetic, but is too irritant in its effect to be practically useful for this purpose.

Circulation.—Strophanthus differs in its physiological action from digitalis in the facts that it is relatively less active as a stimulant to inhibition, probably slightly more diuretic, and less powerful in its influence on the vasomotor mechanism. According to Fraser it affects not only the unstriped muscle but is a poison to the voluntary muscle, primarily increasing its tonicity, and secondarily paralyzing it. When the muscle dies it passes directly into post-mortem rigidity without relaxing.

From a clinical standpoint the most important peculiarities concerning strophanthus are in its absorption and elimination. Although when given by the mouth it appears to act somewhat more promptly than digitalis, the amount of the drug which is absorbed is very uncertain, so that the same dose at one time exercises comparatively little influence upon the circulation and at another may produce toxic disturbances. Moreover, the absorption of strophanthus is probably never complete from the human intestines, for the difference between the intravenous and oral dose is many times larger in the case of strophanthus than with digitalis—probably due to its destruction by the digestive juices. The elimination of strophanthus is comparatively rapid and regular, so that it is less persistent and less likely to cause cumulative effects.

Therapeutics.—Strophanthus is used in practical medicine to meet exactly the same indications as those for which digitalis is prescribed. It is, however, less powerful and less certain in its influence for good than is digitalis, but acts more promptly and more fugaciously. It

would seem to be indicated especially in cases of acute heart-failure; both its tincture and strophanthin are locally too irritant for hypodermic use, but the glucoside has been used intravenously. When actively pushed, it probably is no better borne by the stomach than is digitalis; but experience has shown that some individuals are affected unpleasantly more quickly by strophanthus than they are by digitalis, while in others the opposite is the case. In chronic heart disease strophanthus stands next to digitalis in the list of useful heart tonics and stimulants, in some cases acting more favorably than digitalis for reasons not apparent, in others extremely useful in combination with digitalis, while in the majority of instances it is chiefly advantageous as a remedy to take the place of digitalis when it is from time to time suspended for the purposes of resting the stomach or preventing cumulative action. It is also generally preferred where for any reason it is desirable to avoid an increase in the vascular resistance, and because of its diuretic power it is found of especial value in cardiac dropsy; it is, however, less powerful in its influence upon the kidney than either squill or apocynum.

The glucoside strophanthin being soluble in water affords an excellent means of obtaining the digitalis effect with great promptness in cases of immediate danger. Because of its local irritation it is liable to give rise to much pain if injected either hypodermically or intramuscularly, but the intravenous injection of 1/250 of a grain (0.2 milligramme) of the official strophanthin directly into a vein will often produce the most happy results. This quantity may be repeated in three or four hours if the first dose has not produced the desired effect, but the daily dose should not exceed 1/100 of a grain.

APOCYNUM.

Materia Medica.—Under the name of Apocynum the United States Pharmacopœia recognizes "the dried rhizome of *Apocynum cannabinum* or of closely allied species of Apocynum." Of this genus there are two species indigenous to the United States: the *A. cannabinum,* or dogbane (sometimes incorrectly known as Canadian or Indian hemp), and the *A. androsæmifolium.* These are herbs reaching the height of three to six feet, characterized by their milky juice and pale, greenish-white to pinkish, cymosed flowers.

Finnemore has separated from the *A. cannabinum* a crystalline bitter principle which is neither alkaloidal nor glucosidal, which he calls cynotoxin, and Moore obtained from the *A. androsæmifolium* a principle which he called apocynamarin. Dale and Laidlaw concluded, from a physiological study, that these substances were identical, but Impens asserts that neither one of them is a pure principle, and that the true active principle of the plant is the substance which he calls cymarin, discovered by Taub and Fickewirth.

Physiological Action.—*Local.*—Locally, apocynum is distinctly irritant to mucous membranes, producing in large doses nausea and even

vomiting, with catharsis. According to the work of Dale and Laidlaw, this irritant effect does not reside in the active principle, but in some secondary ingredient.

Circulation.—Apocynum possesses all the characteristic powers of the digitalis group upon the circulation, slowing the heart, increasing the force of its contractions, and causing a contraction of the blood-vessels. The effects, however, upon the pneumogastric nerve are disproportionately strong, so much so that even after large doses the slowing of the pulse is frequently sufficient to counterbalance the other actions of the drug, and it may fail to produce any rise of blood-pressure.

Apocynum appears to act as a direct stimulant to all unstriped muscle-tissue, as well as to that of the blood-vessels.

It is probably the most actively diuretic of the digitalis group. Whether or not the diuresis is brought about by a direct stimulant action upon the secreting structure of the kidney, or whether it is due simply to the increased circulation through the organ is uncertain; but despite the contrary conclusions of Dale and Laidlaw I am inclined to believe it an action on renal epithelium. In my own experiments the vessels of the kidney were uniformly contracted by the drug, but according to Dale and Laidlaw this constriction of the renal vessels is followed by a secondary dilatation, and it is during this stage of vascular relaxation that there occurs the increase in the flow of urine.

Therapeutics.—Apocynum has long been recognized in this country as one of the most active diuretics of this group of drugs; indeed so powerful is its influence in dropsical conditions that it has been referred to by some of the older writers as the "vegetable trocar." Although its chief value is in the dropsies due to cardiac failure, it has also been recommended in the ascites of hepatic cirrhosis. Up till comparatively recently it had not been extensively employed in cases of heart disease not associated with œdema, but within the last few years several writers have commented very favorably upon it as a cardiac tonic, even asserting that it is more reliable than digitalis itself. One great obstacle to its wider employment has been its extraordinary liability to nauseate when given in even moderately full dose. It is asserted that the active principle is borne by the stomach much better.

The only official preparation is the fluidextract, the dose of which is from 5 to 15 minims.

SQUILL.

Materia Medica.—The bulb of *Urginea maritima,* a liliaceous plant growing in the south of Europe, especially on the shores of the Mediterranean. The bulb varies in size from that of a child's head to that of the fist. It is composed of numerous layers or scales, which separate when it is sliced for drying. As kept in the shops, squill is in horny flakes, of a white or red color, becoming leathery when wet,

and having an acrid, bitter taste. It yields to water and alcohol and also to vinegar.

The nature of the active principle of squill has not been established. A number of glucosides have been described by chemists, and Merck has put upon the market three substances, *scillin, scillipicrin,* and *scillitoxin.* There is, however, no sufficient proof as to which, if any, of these substances represents the crude drug.

Official Preparations:

Scilla .....1 to 3 grains (0.06–0.2 Gm.).
Fluidextractum Scillæ .....1 to 3 minims (0.06–0.2 mil).
Tincture Scillæ (10 per cent.).....10 to 20 minims (0.6–1.2 mils).
Acetum Scillæ (10 per cent.).....10 to 20 minims (0.6–1.2 mils).
Syrupus Scillæ (4½ per cent.)..... ½ to 1 fluidrachm (2–4 mils).
Syrupus Scillæ Compositus (Squill and Senega each 8 per cent., tartar emetic ⅛ per cent.) [Coxe's Hive Syrup].....½ to 1 fluidrachm (2–4 mils).

Local Action.—In its local irritant effect squill stands midway between digitalis and apocynum. In overdose it causes vomiting; it was at one time even used for this purpose clinically.

Circulation.—Squill possesses a powerful digitalis-like action upon the circulation. It has an action upon the blood-vessels which is apparently greater than that of digitalis. Its effects, however, upon the circulation do not appear to be as permanent as the latter drug.

Kidney.—With the possible exception of apocynum, squill has more effect in increasing the quantity of urine than any of the other drugs belonging to the digitalis series. It is probable that its effects are due not only to the action upon the circulation but also to a direct stimulant effect upon the renal epithelium; there is, at least, a wide-spread belief among clinicians that in acute inflammatory conditions of the kidney squill may prove highly irritant. According to Pic and Bonnamour it has a disproportionately strong influence in augmenting the elimination of urea in cases of kidney failure.

Therapeutics.—Because of this very marked action upon the kidneys squill is rarely used where a simple digitalis effect is desired upon the heart. On the other hand, in cases of heart-disease associated with œdema, where the kidney is not the seat of an active inflammatory process, squill is one of the most valuable remedies we have. It is also largely used for the evacuation of serous effusion in the pleura or pericardium dependent upon chronic inflammation of the membrane. In cases of dropsy due to nephritis, however, it must be used only with the greatest caution, because of the danger of local irritation of the kidney.

Squill is also used occasionally as an expectorant in the latter stages of acute bronchitis; its favorable influence in this condition depends chiefly upon its local irritant, nauseating effect, although perhaps the increase in the circulation may tend to restore tone to the dilated blood-vessels; as a nauseant expectorant it is certainly inferior to a large number of other drugs.

The best preparation of squill is either the powdered squill itself or the tincture. Neither the fluid extract nor the vinegar completely represents the drug.

In addition to the drugs already described, a few other digitalis allies deserve brief mention.

ACOCANTHERA.

Several native tribes of East Africa prepared an arrow poison which is known as *wabayo,* from various species of the genus *Acocanthera,* which belongs to the botanical family of the *Apocynaceæ.* There has been considerable discussion as to the principles to which these plants owe their activity. According to Lewin, there are two glucosides contained in the various species of this genus which he designates amorphous and crystalline ouabain; they appear to be isomeric. The amorphous ouabain has also been known as abyssinin, while the crystalline variety Lewin considers identical with the acocantherin of Fraser and also with the glucoside found in *Strophanthus gratus.* For this reason it is frequently known as "strophanthin G," which is unfortunate, as it leads to confusion with the official strophanthin, which is approximately half as powerful. Ouabain, while not recognized in the body of the Pharmacopœia, is included among the tests for the purpose of standardizing frogs in the assay of digitalis and allied drugs. The crystalline ouabain has been used as a cardiac tonic, especially for intravenous injection in doses of 1/200 to 1/300 grain (0.3–0.5 milligm.).

HELLEBORUS NIGER.

This plant is found in the mountainous regions of Southern Europe and is widely cultivated. Because its flowers expand in mid-winter it is popularly called Christmas Rose. The rhizome, which was at one time recognized by the United States Pharmacopœia, contains a soluble glucoside helleborein. This glucoside is irritant to mucous membranes and acts upon the circulation much like digitalis, except that it has but little effect on inhibition. It is also asserted by Benturini and Gaspairini to be a powerful local anæsthetic and practically useful in various eye diseases. The dose of the powdered root is from two to three grains (0.1–0.2 Gm.). In large dose Hellebore like Apocynum is an active cathartic and is also prone to produce vomiting.

ANTIARIS.

The *Antiaris toxicaria* is the famous Upas tree of the ancients to which legend attributed a poisonous exhalation so powerful that birds flying over the tree were killed. Although this folk-tale greatly exaggerated the activity of the plant, it is true that it exhales some kind of poison which acts upon the skin of sensitive persons much after the manner of the familiar poison ivy. This tree is a native of the East India Islands and from its gum-resinous exudation was prepared by the aborigines an arrow poison. It contains a glucoside, antiarin, which belongs physiologically to the digitalis group.

CONVALLARIA.

Materia Medica.—The rhizome with the roots of the lily of the valley (*Convallaria majalis*) contains two active substances, convallarin and convallamarin. According to Marmé, the first of these, when taken in doses of 3 or 4 grains, acts as a simple purgative. The soluble glucoside convallamarin, however, arrests the frog's heart in systole and seems to possess the other characteristic properties of digitalis, but its physiological action has not been studied in detail.

Lily of the valley has been used clinically in the treatment of chronic heart disease, especially when associated with dropsy, and was formerly official. The dose of the fluidextract is from 5 to 15 minims (0.3–1.0 mil).

ADONIDIN.

This is a glucoside obtained from the *Adonis vernalis*. The investigations of Cervelo, Hare, Bubnow, Guirlet, and others show that it is to be classed among the digitalis group. According to Kakowski, adonidin differs from the other members of the group in that it relaxes instead of contracting the coronary arteries.

Therapeutics.—In 1879 *Adonis vernalis* was introduced as a cardiac stimulant by Bubnow. The general testimony is that its action in disease resembles that of digitalis, and that it is useful in the same class of cases. It is much more prompt than is digitalis, and Durand affirms that it has no cumulative tendency. There has been some difference of opinion in regard to its diuretic action, and whatever of such influence it has must be attributed to its action upon the circulation in the kidneys rather than to any marked direct power over the secreting structure. Bubnow employed the infusion made from the whole herb, four to eight parts in one hundred and eighty parts of water, and of this he administered a tablespoonful every two hours. Durand gives the dose of adonidin as 0.02 centigramme (one-third of a grain) every three or four hours.

ERYTHROPHLŒUM GUINEENSE.

The bark of this African tree was used by the natives as an ordeal poison. It contains a principle erythrophlein which differs from the other members of the digitalis group in that it is an alkaloid. It appears, however, to be also allied to the glucosides. Like several other of the digitalis principles erythrophlein is a local anæsthetic but is of little practical value for this purpose. The fluid extract of the bark may be given in doses of from 2 to 6 minims (0.12–0.4 mil); the alkaloid is given in doses of from 1/30 to 1/20 of a grain (2–4 milligm.).

BARIUM.

The soluble salts of barium, notably the chloride, have been suggested for practical use as cardiac stimulants. The element barium is a general muscle poisoning, affecting both the voluntary and involuntary muscle. It causes in the frog a delay in the relaxation of striated

muscle similar to that which is seen after veratrine: it acts on the unstriped muscle, causing increased peristaitic movement of the intestines, also contractions of the bladder, and other organs of this kind. The stimulation of the arterial muscle leads to contractions of the blood-vessels and a consequent rise in the blood-pressure. After small doses the force of the cardiac contractions is increased and after large quantities the heart may be thrown into a spasmodic contraction. Barium seems also to have some effect upon the central nervous system, since convulsions are common in mammalian poisoning. According to Filippi it has a profound influence upon metabolism, increasing the elimination of nitrogen in urine but diminishing the proportion of urea.

Barium has failed to achieve the confidence of clinicians and seems to be a more dangerous remedy than the vegetable drugs of the digitalis group. It is employed, however, to a certain extent by veterinarians in the treatment of colic. The dose for human beings is from one-half to one and one-half grains of barium chloride (0.03–0.1 Gm.).

DIGITALIS.

Cohn, Fraser and Jamieson.....J.Ex.M., 1915, xxi.
Cushny .....J.Ex.M., 1897, ii; Heart, 1912, iv, 33.
Gottlieb and Magnus .....A.E.P.P., 1901, xlviii, 262.
Grünwald .....A.E.P.P., 1912, lxviii, 231.
Hatcher and Eggleston.....J.A.M.A., 1913, lx, 499.
Kakowski .....A.I.P.T., xv, 21.
Kobert .....M.M.W., 1912, 1864.
Kraft .....Schweiz. Woch. f. Chem. u. Pharm., 1911, 162.
Joseph .....A.E.P.P., 1913, lxxiii, 81.
Lawrence .....B.M.S.J., 1914, clxx, 37.
Mackenzie ..... Heart, 1911, ii, 273.
Wood, Jr. .....A.J.P., 1902, vi, 283; T. G., June, 1915.

STROPHANTHUS.

Agassiz .....Heart, 1912, iii, 353.
Bailey.....J.P.Ex.T., 1909, i, 349.
Brauns and Clausson.....J.A.Ph.A., 1913, i.
Fraser .....B.M.J., 1885, ii.
Gottlieb and Magnus.....A.E.P.P., 1901, xlvii, 135.
Kasztan .....A.E.P.P., 1910, lxiii, 405.
Tigerstedt .....Skand. Arch. f. Physiol., 1907, xx, 115.

APOCYNUM.

Dale and Laidlaw .....Heart, 1909, i, 138; Proc. Roy. Soc. Med., Dec., 1909.
Impens .....A.G.P., 1913, cliii, 239.
Schubert .....D.M.W., 1913, xxix, 540.
Tyson .....A.J.M.S., 1908.
Wood .....J.A.M.A., Dec. 24, 1904.

ADONIDIN.

Cervello ..... A.E.P.P., xv, 235.
Hare .....T.G., 1886, 220.
Kakowski .....A.I.P.T., xv, 21.

OTHER DIGITALIS-LIKE DRUGS.

Ewins ..... J.P.Ex.T., 1911, iii, 155 (Squill).
Benturini and Gaspairini ..... B.G.T., June, 1888 (Helleborus).
Lewin ..... B.K.W., 1906, 1583 (Acocanthera).
Straub ..... A.E.P.P., 1901, xlv (Antiaris).

BARIUM.

Brunton ..... P.Tr.R.S.L., 1884, i, 223; Pract., June, 1889.
Carpenter ..... M. News, 1891, lix, 93.
Crawford ..... U. S. Dept. Agriculture, Bull. No. 129, 1908.
Filippi ..... Lo Sperimentale, 1907, lx, 610.
Laborde ..... B.A.M., July, 1891.
Ringer ..... B.M.J., 1893, ii, 265.

The second group of cardiac stimulants includes those drugs which increase temporarily the output of energy of the heart. They differ clinically from the digitalis group in that they are much more fugacious in their effects and that they do not tend to a permanent increase in the cardiac power, but rather call out an expenditure of the reserve power of the heart, and physiologically in that they do not slow the pulse and that in toxic dose they act as secondary depressants, so that the heart is arrested in diastole both in the frog and in the mammal. In this group are classed ammonia, camphor, and alcohol.

AMMONIUM.

Materia Medica.—Ammonia is a colorless, irrespirable, highly irritant gas, of strong alkaline reaction, extremely soluble in water. It is obtained upon a large scale as a waste product in the manufacture of coal-gas, and is official in watery and alcoholic solutions and in various salts.

When ammonia gas is dissolved in water it unites, according to the generally accepted theory, with the elements of water to form the hydroxide of a base, ammonium, similar in its chemical properties to sodium and potassium. Thus $NH_3 + H_2O = NH_4OH$.

This base ammonium possesses marked physiological properties, and eight of its salts are official. In many of these salts, however, the acid radical is so much more important than the basic that they are considered in the articles on their acid constituents. In this article is considered only the action of those salts which are used only for the ammonium ion.

Ammonium hydroxide is known only in the form of its solution. This is colorless, with the characteristic pungent odor of ammonia and an alkaline taste. The concentrated solution is active caustic.

Ammonium carbonate of the United States Pharmacopœia is a mixture of the acid ammonium carbonate and ammonium carbamate and should yield 31.58 per cent. of gaseous ammonia. It has an alkaline reaction and the characteristic odor and taste of ammonia. It occurs in white, translucent, fibrous masses, which on exposure become opaque and efflorescent, parting with both ammonia and carbonic acid. It is soluble in four and a half times its weight of water.

Ammonium chloride, or sal ammoniac, when pure, is a white crystalline powder freely soluble in water, *without odor,* but having a pungent, salty taste. It is neutral or slightly acid to litmus.

Official Preparations:

Aqua Ammoniæ Fortior (28 per cent.).....Not used internally.
Aqua Ammoniæ (10 per cent.) .....15 to 45 minims (1–3 mils).
Spiritus Ammoniæ Aromaticus .....15 to 45 minims (1–3 mils).
Ammonii Carbonas .....5 to 10 grains (0.3–0.6 Gm.).
Ammonii Chloridum [Sal Ammoniac].....5 to 10 grains (0.3–0.6 Gm.).
Linimentum Ammoniæ (35 per cent.).....External use.

Physiological Action.—Ammonium hydroxide, like the other hydroxides, is a powerful local irritant, and in concentrated solution a caustic. This action is due rather to the hydroxyl ion than to the ammonium. With the exception of the carbonate, the other salts of ammonia are not much more irritant than the neutral salts of the alkaline earths.

Nervous System.—Ammonium is a stimulant to the medulla, especially to the vasomotor and respiratory centers, and to the spinal cord. In the lower animals it is capable of causing tetanic convulsions with greatly exaggerated reflexes.

Circulation.—The intravenous injection of ammonium produces a temporary fall of the blood-pressure, due to the fact that when introduced into the circulation in this manner it reaches the heart comparatively concentrated, but this is soon followed by a marked rise of blood-pressure above the norm, which is the characteristic effect of the drug. The rise in blood-pressure occurs after previous section of the spinal cord, and is therefore independent of the vasomotor centers; whether it is due to an effect upon the heart or upon the arterial muscles is uncertain; the probabilities are that both are affected. While the increase in the circulation following the exhibition of ammonium may be quite pronounced, it is very fugacious. It is doubtful whether the physiological action of this stimulant ever lasts more than ten minutes.

Concerning the changes in pulse-rate our knowledge is unsatisfactory, but it would appear that there is at first an increase in the rapidity of the heart's action, but that when the pressure reaches its maximum the heart is slowed, probably reflexly from the increase in pressure.

After a large toxic dose the rise is followed by a fall, and, indeed, if the dose has been sufficiently large and sufficiently rapidly injected, the elevation may be entirely lacking.

Absorption and Elimination.—Although the carbonate and hydroxide of ammonium are readily absorbed from the alimentary canal, they do not produce their characteristic physiological effects when administered through this channel. This is due to the fact that, being crystalloids, they are absorbed directly into the intestinal veins and carried by the portal vein to the liver, where the ammonium is converted into urea;

it is possible that a portion of the base is oxidized into nitric acid. On the other hand, when given hypodermically, ammonium must be carried to the heart and nerve centers before the liver. In the case of the chloride, while a similar decomposition of the ammonium may take place, the hydrochloric acid must be neutralized, and for this reason the body will form more ammonium to combine with the hydrochloric acid, and therefore the practical result will be the circulation of ammonium chloride in the blood.

As the ammonium is oxidized in the body, even the alkaline salts of this base do not diminish the acidity of the urine; indeed there is strong reason to suspect they increase it.

Ammonium hydroxide, although a very volatile substance, is so irritant to mucous membranes that it is irrespirable, and, therefore, cannot be administered by inhalation. The action of smelling-salts in cases of syncope does not depend upon the absorption of the ammonia, but merely upon the reflex excitation of the medulla through irritant action upon the nasal mucous membrane.

Therapeutic Uses.—Externally, ammonium hydroxide is much used as a constituent of irritating liniments, and, on account of its efficiency and cheapness, is very valuable. By inverting a watch-glass full of the stronger water of ammonia upon the skin, a blister may be raised in a very few minutes; but, as the effects of the application are apt to be severe, the use of it is justifiable only under rare circumstances.

Internally, ammonium is largely used for the relief of acute heart-failure, as in shock and collapse. It must be remembered, however, that the drug is not well absorbed through the gastric mucous membrane, and if used, therefore, as a circulatory stimulant, it should be administered hypodermically; or, better, intravenously. When the failure of the circulation depends upon a slow and persistent cause, as in adynamic fevers, ammonia is not generally useful, but may be employed as an adjuvant to alcohol in the crisis of the disorder. As a stimulant, ammonia may be useful in poisoning by venomous serpents, but the statements that have been made that it is antidotal to venom have no foundation. Its action is merely that of a circulatory and respiratory stimulant.

Ammonia appears to have a tendency to act upon the mucous membrane of the lungs, and its salts, especially the carbonate and the chloride, are used as stimulant expectorants in acute bronchitis when free secretion has just been established. In chronic bronchitis it may be administered from time to time when the secretion is not very free. Although there is a widespread belief that ammonium chloride has a specific action upon the respiratory mucous membrane, there is no sufficient data to lead one to consider the theory established. While it is often of service in the treatment of acute bronchitis, it is doubtful whether it has any effect different from the other saline expectorants. Böcker insists that it hastens very greatly the nutritive changes and the exfolia-

tion of the epithelium in all mucous membranes, and highly recommends it in gastro-intestinal conditions.

The statement of W. Stewart, made in 1870, that it is an effective remedy in chronic torpor of the liver and chronic hepatitis, has been sustained by subsequent clinical experience, and it is frequently used in catarrhal jaundice in doses of from twenty to thirty grains well diluted three or four times a day.

The use of the alkaline preparations of ammonia as antacids is considered on page 401.

Toxicology.—The poisonous action of the water of ammonia depends on its local irritant effects, which are due, as has been seen, to the hydroxyl ion. This subject will, therefore, be considered under the hydroxyls. (See page 357.)

CAMPHOR.

Materia Medica.—Camphor is a stearopten which is obtained in China, Japan, and the neighboring islands by boiling the comminuted wood of the root of the *Cinnamomum camphora,* a handsome evergreen tree which sometimes reaches a height of fifty or sixty feet. The camphor which rises to the surface of the boiling water is skimmed off and partially purified by sublimation—coming into commerce as *crude camphor,* which occurs in grains of a whitish or pinkish color—and is finally purified by sublimation with lime.* Camphor is also manufactured synthetically.

Refined camphor (or, as it is commonly called, *camphor*) occurs in disks or hemispherical, bowl-like, translucent masses, of a fibrous or granular fracture. Its taste is hot and peculiar; its odor very strong and characteristic; it is volatile, inflammable, tough, but readily pulverized on the addition of a few drops of alcohol; melts at 347° F.; is soluble in one thousand parts of cold water,† in one part of strong alcohol, and still more soluble in chloroform; thrown upon water, a granule of camphor floats, and exhibits a rotatory movement.

Official Preparations:

Camphora .....5 to 15 grains (0.3–1.0 Gm.).
Aqua Camphoræ (0.8 per cent.).....½ to 2 fluidounces (15–60 mils).
Spiritus Camphoræ (10 per cent.).....15 to 30 minims (1–2 mils).
Camphora Monobromata .....5 to 10 grains (0.3–0.6 Gm.).
Linimentum Camphoræ (Camphor 1 part,
Cotton-seed Oil 4 parts).....External use.
Linimentum Saponis (4.5 per cent.).....External use.

* Borneo camphor, yielded by the *Dryobalanops camphora,* is very highly valued in the East, but does not reach this country. Stockman has found that both it and the *Nagi camphor* of China act on the organism like camphor. (See Pellicani.) A number of other camphors, such as *camphor-cymol, bornylamin, amido-camphor, campherol,* have been examined by various investigators, and found to resemble true camphor very closely in their physiological action.

† By rubbing the camphor up with magnesia in water, the latter can be made to take up much more than one part in one thousand.

Physiological Action.—Camphor, though primarily a local irritant and stimulant, probably has a narcotic action on nerve-endings in the mucous membrane, in this way relieving intestinal spasm. It is slowly absorbed and in great part or altogether oxidized in the organism, probably changed first into camphorol, and being excreted in the urine as campho-glycuronic acid and amido-glycuronic acid (Schmiedeberg and Meyer).

Nervous System.—In the frog large doses of camphor are depressant to the spinal cord and will cause eventually paralysis with loss of reflexes. In warm-blooded animals it gives rise to convulsions which are due to an action upon the motor area of the brain. It also exercises a stimulant effect upon the intellectual centers and is capable of partially overcoming the sleep-producing action of the somnifacient drugs.

In the frog the paralytic action is a descending one, there first being loss of voluntary movement, secondly loss of reflexes, and finally paralysis of the peripheral motor nerves.

Circulation.—Although clinical experience seems to indicate that camphor has a profound effect upon the circulation, our knowledge of its action is incomplete and uncertain. It has been shown by a number of competent investigators that when applied to the isolated frog's heart it decreases the rate and increases the energy of contraction, and it may be considered established that upon the frog's heart camphor acts as a stimulant.

On the other hand, the evidence of stimulation of the heart in mammals is far from satisfactory. At times camphor, when injected in small doses directly into the circulation of a mammal, increases the arterial pressure, but this increase is never constant or persistent and is often absent, the characteristic effect of the camphor being depression of the arterial pressure. It is, of course, possible for a drug to stimulate the heart, and yet so widen the blood-path as to produce no increase in the arterial pressure; but, although Gottlieb, Maki and Lewin believe that they have obtained evidence of cardiac stimulation, other observers have failed to do so. It probably, however, is a stimulant to the cardiac muscles and widens the blood-vessels, partly by an action on the vasomotor centers and partly by a direct influence on the arterial walls.

The above summary of the experiments of the action of camphor upon the circulation fails to explain the extraordinary effects which sometimes follow its use in clinical medicine. There is, however, experimental evidence that in various diseased conditions its action on the heart is more positive. Thus Heubner has shown that it will re-excite movement of the frog's heart when arrested by muscarine, Boehme that it causes the heart arrested by chloral to recommence beating, and Leo states that in experimental phosphorus poisoning camphor produces a distinct rise in the blood-pressure. Seligmann has shown that in the cat, and Gottlieb that in the dog, the liability of fibrillation of the heart is much reduced.

Respiration.—Moderate doses of camphor stimulate respiration, increasing both its rate and depth. The asphyxia of advancing camphor poisoning indicates that the respiratory centers finally share with the motor centers of the spinal cord the paralyzing influence of the overwhelming dose of the drug.

Camphor appears in some way to either prevent the growth of bacteria in the body or at least to lessen the harmful effects of their toxins. A number of investigators have found that in rabbits the intravenous injection of camphor greatly lowers the mortality after pneumococcus infections.

Therapeutic Uses.—Camphor is used in medicine for four purposes: (1) as a circulatory stimulant, (2) as a nerve sedative, (3) in the treatment of diarrhœas, and (4) as a local stimulant.

In conditions of grave depression of the heart camphor has proved itself one of our most reliable remedies. It is especially useful in the later stages of infectious fevers, as pneumonia or septicæmia. The effects of camphor in these conditions at times seem marvellous, but are of comparatively short duration, lasting generally about an hour, or perhaps two. By the repeated use of the drug, however, in conditions in which one may reasonably hope for a natural change for the better in a few hours, such as is seen typically in pneumonia, camphor may enable us to tide over the patient till the crisis and thus avert an otherwise fatal issue. As a circulatory stimulant camphor must always be given hypodermically, as it is absorbed too slowly from the alimentary tract to exercise any action on the circulation; five grains may be dissolved in a half drachm of olive oil and injected every two hours as needed.

As a nerve sedative camphor has enjoyed a considerable reputation for the relief of those conditions of nervous excitability which find their full expression in hysteria. Whether it has any direct action on the central nervous system or owes its effects entirely to its taste and local irritant action on the gastric mucosa is uncertain. It has also been used in sexual excitements and various forms of convulsions, but with doubtful benefit.

In diarrhœas of the serous type (see page 77) camphor is often a useful drug. It probably acts as a local stimulant to the mucous membrane, and is usually used in conjunction with opium.

Externally, camphor is widely employed as a mild counter-irritant, chiefly in the form of the camphor liniment, which is popularly known as "camphorated oil." It is also employed as a local remedy in the treatment of inflammatory conditions of the nose and throat, dissolved in liquid petrolatum.

ALCOHOL.

Materia Medica.—Absolute alcohol—*i.e.*, ethyl alcohol containing not more than one per cent. by weight of water—is a colorless, volatile liquid, boiling at 172° F., not congealed by a cold of —166° F., and having the specific gravity of 0.797. It is used only for chemical purposes. Alcohol of the Pharmacopœia contains 94.9 per cent., by volume,

of absolute ethyl alcohol, and has the specific gravity of 0.816; diluted alcohol contains 48.9 per cent., by volume, of absolute ethyl alcohol.

Alcohol also occurs in larger or smaller amounts in a number of beverages. Any fruit which is capable of yielding fermentable sugar may be used as the source of an alcoholic beverage. Practically, however, the great mass of alcoholic beverages which are used in this country are prepared either from cereal grains or grapes. The germination of grains such as rye and corn leads to the transformation of their starch into a peculiar sugar, known as maltose. The resultant mixture is the substance known as malt. This, when fermented and flavored with infusion of hops, is the basis of the so-called malt liquors, which include beer, ale, porter, brown stout, etc. These contain from two to six per cent.—occasionally more—alcohol. The distillate from malt liquors yields the substance known as whiskey,* the varieties of which are named according to the grain used for their manufacture, as corn whiskey, rye whiskey, etc. The liquor resulting from the fermentation of grape juice is known as wine. Red wine is made from purple grapes, allowing the fermentation to be carried on in the presence of the skins, extracting thereby a considerable quantity of the coloring matter and also of the tannin, which is contained in the grape skin. For this reason red wines generally contain larger proportions of tannic acid than white wines. The wines range in alcoholic content from 8 per cent., for clarets, to as high as 20 or 25 per cent. in port wine and sherry. The result of the distillation of wine is brandy, which is sometimes designated as cognac brandy to distinguish it from brandies made from other fruit juices. Among the less commonly employed alcoholic beverages may be mentioned hard cider, which is made from apple juice, and its distillate, commonly known as apple jack; rum, which is made by distilling the fermented juice of the sugar cane; agua miele, a liquor made in Mexico from the juice of a species of aloe; and saki, a Japanese whiskey made from rice. Liqueurs are strong alcoholic beverages which are artificially flavored by the addition of various volatile oils. Under this definition would be included gin, which contains as one of its essential ingredients the oil of juniper.

Many of the alcoholic beverages have from time to time been recognized by the U. S. Pharmacopœia, but in the Ninth Revision these were all omitted. The necessity of pharmacopœial standards no longer exists, as these are provided by the U. S. Department of Agriculture.

Alcohol is widely employed in pharmacy, both for the purpose of extracting the activity from vegetable drugs and as a preservative of other preparations. The fluidextracts and tinctures of the United States Pharmacopœia contain generally from 30 to 40 per cent. of alcohol.

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* Much of what is sold as whiskey is an artificial liquor made by coloring and flavoring raw alcohol. In the opinion of the author, however, the term "whiskey" should properly be applied only to the unadulterated distillate from fermented grain.

Physiological Action.—In strong solution alcohol is a protoplasmic poison and, therefore, is capable of acting as a germicide. It differs from other germicides in that its power is not always proportionate to its concentration. It has been shown that the greatest bactericidal effect is obtained from a solution containing approximately 70 per cent. of alcohol. Higher concentrations are no more powerfully germicidal; indeed, in the absence of moisture, because of their dehydrating influence, are much less so.

Circulation.—There has been a great deal of acrimonious dispute concerning the action of alcohol upon the circulation. For several years pharmacologists and clinicians held diametrically opposite views concerning the influence of this drug upon the heart, the former asserting that it had no stimulant action upon this organ, the latter classing it as one of the most valuable cardiac stimulants we possess. Gradually, however, the views of the scientists and the practitioners are growing closer and closer; the clinicians of to-day hold alcohol in much less esteem as a circulatory stimulant, and the majority of pharmacologists granting that it has some influence in increasing the heart's action.

When alcohol is introduced into the blood stream in moderate quantities alteration in the blood-pressure is insignificant, and if larger doses are given it produces a fall. It must be remembered, however, that the blood-pressure is the result of two factors—the driving of the pumping force of the heart and the resistance offered by the blood-vessels—and it is at least conceivable that these two factors might act antagonistically and so counterbalance each other. Strong evidence in favor of an effect of this kind from alcohol is found in the observation, originally made by Castillo and confirmed by Abel and by Wood and Hoyt, that after section of the spinal cord and consequent destruction of the vasomotor influence of alcohol the drug produces uniformly an increase in the pressure. Further support for the truth of this belief is the increase in the rate of flow through the blood-vessels under the influence of alcohol. It is evident that the rapidity with which the blood flows through the arteries increases with the increase in the heart's action and diminishes with decrease in the calibre of the vessels. The fact that alcohol makes the blood flow more rapidly, therefore, shows that either it increases the heart's action or widens the blood-vessels, or else does both. While most of the early investigators who studied the action of alcohol on the isolated heart of either the frog or mammal failed to obtain any evidence of an increase in its functional activity as the result of the administration of alcohol, this failure has been apparently due to the lack of delicacy in the methods employed. Nearly all of the recent studies of the action of alcohol upon the heart either of the warm-blooded or cold-blooded animal have shown from small quantities a distinct, if not remarkably large, increase in the output of this organ. According to Dixon, this stimulant influence is most marked when the heart is partially exhausted from lack of nutrition, and he believes

that alcohol acts largely by providing the cardiac muscle with an easily combustible, energy-providing nutrient.

Concerning the effects of large doses of alcohol there is no disagreement, it being universally conceded that it exercises a depressant influence on both the heart and the vasomotor apparatus. The dilatation of the vessels is most marked in the skin area.

The dose of alcohol which has been found to stimulate the heart would correspond to a quantity about equivalent to one-half to one fluidounce of whiskey for a man.

Nutrition.—The experiments which have been carried out concerning the effect of alcohol on the metabolism of the body, although extraordinarily numerous and complex in their methods, have been so contradictory in their results as to render final conclusion concerning the effects of the drug on the nutritive processes of the body almost impossible. Certain facts, however, seem to be well established. These may be summarized as follows: When a moderate quantity of an alcohol beverage is ingested, equivalent to not more than an ounce or two of alcohol, about 90 to 95 per cent. is completely oxidized in the body, being eliminated finally as water and carbonic acid gas. When the quantity is larger the proportion which is burnt up in the system becomes less. All processes of oxidation yield energy, and the oxidation of so considerable a quantity of a substance of such a high caloric value as alcohol should yield to the system an amount of energy sufficient to be determined. It has been experimentally proved, both in lower animals and in man, that the energy which is derived from the combustion of alcohol can be successfully utilized by the animal economy. Thus in an animal in a state of metabolic equilibrium, whether at rest or undergoing physical exertion, a portion of the carbonaceous food may be replaced by an equivalent quantity of alcohol without disturbing metabolism. It is evident, however, that the quantity of food which can be replaced by the alcohol is limited by two facts—first, that the system oxidizes only with difficulty large quantities of the drug, and, secondly, by the fact that if too freely indulged in we get its poisonous narcotic action. The amount of alcohol which can be economically utilized in the body varies greatly under different circumstances; for instance, in febrile conditions much larger quantities can be consumed than in healthy individuals. The average amount which can be taken care of by the ordinary healthy man is somewhere in the neighborhood of three ounces of absolute alcohol in the twenty-four hours.

Whether alcohol has any direct influence on the nitrogenous metabolism is at present a matter of much difference of opinion and concerning which, it seems to me, it is impossible to draw final conclusions. It is evident that if for any reason the body is unable to derive sufficient energy for its daily needs from the carbonaceous portion of the food supply there must be a call upon the reserve stored up in the system in the form of glycogen or fat or of nitrogenous

products, and that under these circumstances, therefore, alcohol may act as a nitrogen-conserving food. On the other hand, when the quantity of food is ample and the power of assimilation normal alcohol does not decrease the nitrogenous output. Moreover, according to several authorities—although the matter cannot be considered finally settled—while the total quantity of nitrogen excreted is not greatly affected by alcohol there is a change in the form in which the nitrogen is eliminated; thus a number of investigators have found that there was a relative increase in the output of uric acid with a compensating diminution in the output of urea.

Muscular System.—Although there is some contradiction in the experimental results the bulk of the evidence seems to indicate very strongly that alcohol in moderate quantities increases the capacity of the muscle for work. This appears to be true whether the drug be applied directly to the isolated frog's muscle or tested upon human beings by means of the ergograph. Whether this favorable influence upon muscular work is due to the food value of the alcohol or is a strictly drug action is as yet not manifest.

Digestion.—In considerable quantities, ten per cent. or over, alcohol interferes with the chemical activity of the peptic ferments, and if sufficiently concentrated will entirely destroy their power. The effects of alcoholic beverages upon artificial digestion are not dependent solely upon the alcohol which is in them, for the distilled liquors are much less injurious in proportion to the percentage of alcohol than the wines, and these in turn are less so than the malt liquors. While large quantities of alcohol lessen the chemical activity of pepsin, small amounts are without any appreciable effect upon artificial digestion. But when we consider the effects on the digestive processes within the body it is necessary to take into consideration not only the effects upon enzyme activity but also upon the secretion of digestive juices. There is no room for doubt that small quantities of the alcoholic beverages, at least of the distilled liquors, increase the secretion not only of the gastric glands but also of the salivary glands, and perhaps of the digestive ferments in the intestines. This effect appears to be two-fold in nature: first, due to a local irritant action upon the mucous membrane of the mouth and stomach, and, secondly, a specific action, for it has been shown that the administration of alcohol by the rectum will in both the dog and man cause a more profuse secretion of the gastric glands.

Therapeutic Uses.—Alcohol is used in medicine for four purposes: (1) As a cardiac stimulant, (2) as an accessory food, (3) to stimulate digestion, and (4) as a local remedy.

As a stimulant to the circulation alcohol is serviceable in cases of temporary heart-failure. When there is marked widening of the blood-vessels, alcohol is only of secondary value, because with marked relaxation of the blood-vessels no degree of heart stimulation is capable of elevating the blood-pressure. It is essential in conditions of vasomotor weakness that tone be restored to the dilated blood-vessels

through the use of vasomotor stimulants, and, therefore, in this type of circulatory depression, alcohol, whilst sometimes of service as an adjuvant, cannot be relied upon by itself to maintain the circulation.

As a food-stuff alcohol is especially of service in those conditions where the powers of assimilation are below par and the system is unable to utilize the ordinary foods. Under these circumstances it offers to the economy an easily oxidizable substance which requires no previous preparation on the part of the digestive organs for absorption. It must be remembered, however, that in the first place it can in no way replace the nitrogenous elements of the food, and in the second place the quantity which can be taken is limited by what we might speak of as the drug action, and at best it can only replace a portion of the carbonaceous food elements.

As a stimulant to digestion alcohol is of service in all cases of digestive failure not dependent upon inflammatory conditions of the gastro-intestinal tract. In chronic digestive failure, although it is capable of proving beneficial, it is a remedy which is to be used with great caution, if at all, on account of the danger of the formation of a habit. It finds its chief field of usefulness as a digestive stimulant in low fevers, such as typhoid, where the digestive functions are in abeyance and the duration is self-limited.

One of the most important uses of alcohol is in the treatment of adynamic fevers, such as typhoid, typhus, septicæmia, and asthenic pneumonia. Its value in these conditions is due to a combination of the three effects just described. Perhaps its practical utility can be most clearly explained by taking a concrete example. In typhoid fever, for instance, one of the most threatening dangers is exhaustion due to the increased oxidation going on in the body, the result of the high temperature, and to the comparative feebleness of the digestive organs, making it difficult for the system to utilize the ordinary food-stuffs in large enough quantity to meet the needs of the organism. Under these circumstances alcohol, if properly used, by its stimulant influence upon the digestive secretions increases the power of the body to avail itself of the food-stuffs which require digestion, and, secondly, by its easy oxidizability protects the reserve supply of the body stored up in the form of glycogen and fats from destruction. In order that advantage may be derived from its stimulant influence upon the digestive tract it is evident that the alcohol should be administered at the time other nourishment is being taken, and since, if taken too freely, it not only interferes with digestion but is itself an uneconomical food-stuff, the quantity should be limited. Ordinarily about two drachms may be administered every two or three hours, according to the intervals for feeding. In the latter stages of the fever, when the circulation begins to react from the primary stimulation brought about by the high temperature, the stimulant action upon the heart also adds to its value. A question of great importance in this connection, but one which cannot yet be considered to be finally settled, is the influence of alcohol upon the resistance of the body to bacterial

invasions. It seems established with a fair degree of certainty that large doses of alcohol increase the susceptibility of the body to infections, but the evidence concerning the influence of therapeutic doses is insufficient to be conclusive.

Another effect of alcohol which probably contributes to its value in these infections is its narcotic action. Even relatively small doses in persons not accustomed to its use diminish the acuteness of perception of uncomfortable sensations, and in this way tend to prevent the exhaustion of the strength which is always a consequence of suffering.

As a circulatory stimulant alcohol has enjoyed an extraordinary popularity in the treatment of various poisonings, especially snake bite. While it is possible that reasonable amounts of alcohol may be of some value in snake bite, there is little doubt but that more persons bitten by venomous serpents have been killed by the inconsiderate use of the remedy than by the poison of the snake. There are many circulatory stimulants which are vastly superior to alcohol, and the old superstition that a man would invariably recover from snake bite if it were possible to intoxicate him with alcohol is a foolish error which has been the cause of many deaths.

As a relaxant of the peripheral circulation alcohol is especially useful in short minor infections which follow exposure. It lessens the danger of catching cold by dilating especially the vessels of the skin, which tends to prevent the occurrence of internal congestions. Also, by virtue of its effect upon the vessels of the skin, it has more or less sudorific power, and is widely used in connection with other remedies as a diaphoretic in the early stages of minor fevers.

As a local remedy alcohol is of service in a variety of surgical conditions. It is of value not only because of its antiseptic influence, but in some way it seems to lessen the pain of acute inflammations even where there are no bacteria present.

SPARTEINE.

The United States Pharmacopœia formerly recognized under the name of scoparius the tops of the broom plant (*Cytisus scoparius*). This contains two principles—one a neutral principle, scoparin, and the other a liquid alkaloid, sparteine. The latter is still recognized by the Pharmacopœia under the form of the sulphate.

Sparteine sulphate occurs in colorless, prismatic crystals freely soluble in water or alcohol, with a bitter, slightly saline, taste.

Physiological Action.—The results of different investigators of the action of sparteine have been so extraordinarily divergent, especially as regards its effects on the circulation and kidneys, that it is almost impossible to escape the conviction that there is more than one substance which has been used under this name. A number of capable experimenters have found that the alkaloid is a powerful stimulant to the heart and causes a marked rise of blood-pressure.

Equally careful pharmacologists, however, have failed to obtain any true stimulation of the circulatory apparatus. According to this latter group of investigators, the most important action of sparteine is a paralytic effect upon the peripheral ends of the motor nerves.

Equally contradictory have been the statements concerning the action of sparteine upon the kidney. MacNider in one series of experiments failed to obtain any influence upon the kidneys, but in a second series in which another sample of the alkaloid was used, and in larger doses, there was a marked diuretic effect.

Therapeutic Uses.—The results of clinicians with sparteine are as contradictory as those of pharmacologists. On the one hand, a number of competent observers have found the drug of much value in the treatment of chronic cardiac affections, affirming that it makes the pulse slower and more regular and has a pronounced effect in increasing the flow of urine, while other observers have failed to obtain any beneficial influence from the drug whatsoever in these disorders. In my own experience sparteine has not proven of value. In the light of the confusion which at present exists concerning the action of this drug its use must be largely experimental.

The doses which have been recommended are almost as much at variance as the statements concerning the effects. Many physicians assert that they obtained beneficial results from ¼ of a grain (0.015 Gm.), while others state that it is useless to give less than one or two grains at a dose (0.06–0.10 Gm.).

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DRUGS WHICH STIMULATE THE VASOMOTOR MECHANISM.

The importance of vasomotor tone in maintaining blood-pressure is frequently overlooked, but many cases of sudden death—such as have followed severe blows upon the abdomen—are undoubtedly due to acute paralysis of the blood-vessels, and the evidence is strong that many conditions, such as surgical shock and the circulatory weakness in the latter stages of infectious diseases, which were at one time considered to be due to heart-failure, are more likely to result of vascular dilatation. It is a physiological byword that the blood-vessels of the abdomen alone are sufficient to contain all the blood of the body, and it is evident that if these vessels were dilated to their full capacity, no matter how vigorously the heart might contract, it could not maintain the circulation of the blood, for it would simply be pumping whatever blood came to it into a huge reservoir which it is impossible to fill. The old expression of "bleeding a man into his own arteries" conveys a clear concept of what happens under these circumstances. It is manifest, therefore, that in cases of vasomotor paresis the cardiac stimulants can be of little service unless assisted by a vasomotor stimulant. On the other hand, however, under most conditions of acute circulatory failure, if the vasomotor system will respond, cardiac stimulants are hardly necessary. Unfortunately, in many instances the vasomotor system is so profoundly affected that it refuses to respond, at least in anything approaching a normal degree, to stimulating drugs, especially to those which act centrally. Under these conditions much benefit may be derived from the intravenous injection of physiological salt solution. The action of this is purely mechanical, increasing the quantity of fluid in the vessels to correspond to their enlarged capacity, so that there is some chance for the heart to keep up circulation.

The dominant vasomotor centers are located in the medulla oblongata, and we find that most of those drugs which affect the vasomotor center act also upon other medullary centers, notably the respiratory; they are also generally stimulants to the spinal cord.

Besides acute vasomotor paresis giving rise to dangerous circulatory failure, there are many states which are probably dependent on a chronic feebleness of the vasomotor mechanism. These conditions generally manifest themselves by the secondary consequences of vascular dilatation. Examples of these are seen in the night-sweats

occurring in conditions of chronic debility, such as phthisis, and in certain types of diarrhœas.

Drugs may increase the vascular tone, either by acting upon the vasomotor centers or by acting directly on the walls of the blood-vessels. Among those whose action is central may be mentioned especially strychnine, digitalis, atropine, and cocaine; all except the first of these are considered elsewhere in this work. The peripherally acting vasoconstrictors include epinephrine, ergot, hydrastis and the extract of the pituitary gland.

NUX VOMICA.

Materia Medica.—The seeds of *Strychnos nux-vomica,* a middle-size tree growing in the East Indies and Australia, whence the drug enters commerce. The fruit of the nux-vomica tree resembles externally the orange. Each fruit contains four or five seeds. These are circular, nearly flat disks, a little less than an inch in diameter, covered with very short, satin-like, grayish hairs; internally they are tough and horny, and are possessed of an intensely bitter taste. The effects of nux vomica are due chiefly to the alkaloid strychnine, although it contains another alkaloid of physiological activity, brucine. These alkaloids exist in combination with an acid, the so-called igasuric of Pelletier and Caventou, which, according to Husemann, is identical with malic acid. It is usually estimated that strychnine constitutes about forty per cent. of the alkaloids. Practically there is no qualitative difference between the medical action of strychnine and that of the cruder preparations of nux vomica, over which it usually should have the preference on account of definiteness of action. The U. S. Pharmacopœia directs that nux vomica shall contain at least 2.5 per cent. of total alkaloids.

As kept in the shops, strychnine is a grayish-white powder, but may be obtained in octahedral or quadrilateral prisms. It is so bitter that it will impart an intensely bitter taste to seven hundred thousand times its weight of water. On account of its insolubility (one in about three thousand parts of cold water) it is very rarely used in medicine, at least in the United States, the sulphate being universally preferred, and being what is commonly meant in American writings when the word "strychnine" is used. Strychnine sulphate contains about seventy-five per cent. of strychnine.

Official Preparations:

Extractum Nucis Vomicæ (16 per cent. of alkaloids) ..... ¼ to ½ grain (0.015–0.03 Gm.).
Fluidextractum Nucis Vomicæ..... 1 to 3 minims (0.06–0.18 mil).
Tinctura Nucis Vomicæ (10 per cent.)..... 10 to 30 minims (0.6–2.0 mils).
Strychnina .... 1/60 to 1/20 grain (1–3 milligm.).
Strychninæ Sulphas ..... 1/60 to 1/20 grain (1–3 milligm.).
Strychninæ Nitras ..... 1/60 to 1/20 grain (1–3 milligm.).

Physiological Action.—The effect of strychnine is to stimulate the centers of the lower portion of the central nervous system, affecting both the spinal cord and the medulla, the action, however, being more marked upon the former.

Spinal Cord.—In moderate doses strychnine in both the frog and the mammal leads to an increase in the reflex excitability. At first this action leads simply to an exaggeration of the normal reflex action, but in larger quantities it gives rise to violent convulsions. Since these convulsions occur in de-cerebrated animals, they must be of spinal origin.

Although in an animal poisoned with strychnine the susceptibility of the spinal cord is sometimes so great that it would appear as though the convulsions arose spontaneously, closer examination of the conditions will show that these convulsions are always of reflex origin; that is, that it requires some kind of sensory impulse to provoke the motor outburst. The excitability of the spinal cord is so great that irritations which are too slight to be ordinarily perceptible, either to the reflex centers or to consciousness, are sufficient to provoke a convulsive response in the strychnized animal; thus a loud noise or a puff of air may be the beginning of a violent convulsion. Not only is the motor response brought about by extraordinarily feeble afferent causes, but it is greatly altered in character. If a de-cerebrated unpoisoned frog is suspended and a solution of dilute acid brought in contact with the foot, the foot is gently drawn away from the acid. If the strength of the acid is somewhat greater, then, although it may be applied only to one foot, both feet will be drawn up. Now if the same frog is given a dose of strychnine, instead of drawing the foot away from the acid the legs will be violently extended and the whole animal become rigid, remaining so for a period of several seconds. In other words, not only is there a change in the vigor of the reflex response, but a disturbance, so to speak, of its co-ordination. This is due to the fact that strychnine so excites the spinal centers that sensory impulses which ordinarily reach only the nearest motor ganglion are spread throughout the whole spinal cord, so that, instead of a single muscle group being involved in the reflex, every muscle of the body responds with its full power. The position which will be assumed by the animal will depend solely upon the comparative power of opposing muscle groups; thus in the frog the hind legs are violently extended because the extensors are much more powerful than the flexors, the mouth is usually drawn open and the forelegs half bowed. In the man the arms are rigidly flexed because of the power of the biceps, the legs extended, the body arched backward, and the jaw firmly closed.

There has been some difference of opinion as to whether strychnine acts upon the sensory or motor tracts of the spinal cord. If strychnine be applied to one portion of the spinal cord, say the upper half, and an afferent nerve running to this part is stimulated, then convulsions

are caused throughout the body, but if some portion of the body whose nerves pass to the unpoisoned section are stimulated, we get merely an ordinary normal reflex; in other words, a sensory impulse received in the poisoned section of the cord leads to convulsions all over the body. This fact is only to be explained on the theory of a hyper-excitability of the receptive centers of the cord. Recently it has been shown by Ryan and McGuigan that when strychnine is applied to the lower portion of the spinal cord electrical irritation of the motor area in the brain which is too weak to lead to any response in the upper or unpoisoned portion of the spinal cord gives rise to

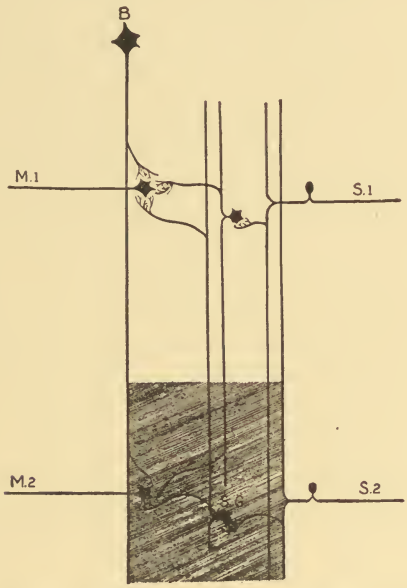

FIG. 18.—Diagram to explain that the action of strychnine is on both the receptive and motor centers. M. 1, Motor nerve to fore-leg; M. 2, motor nerve to hind-leg; S. 1 and S. 2, sensory nerves from fore- and hind-legs; S. G., receptive ganglion in the spinal cord. The shaded portion of the spinal cord has been poisoned by strychnine, the unshaded not. If S. 1 be stimulated we get an ordinary reflex movement in the part supplied by M. 1, but if S. 2 be stimulated we get a general convulsion involving both M. 1 and M. 2; therefore the poisoned ganglion S. G. must be sending out abnormally strong impulses, otherwise the root-cell of M. 1 would not be affected. This proves that strychnine acts on the receptive centers in the cord. On the other hand, when the motor cells of the brain (B.) are stimulated with a weak current there is a contraction of the muscle supplied by M. 2 but not in that supplied by M. 1; therefore, the root-cell of M. 2 must have had its irritability increased by the strychnine. Strychnine excites both the receptive and motor cells of the spinal cord.

movements in the hind legs. Since the pathway from the centers of the brain to the muscle does not in any way involve the sensory ganglia, this hyper-excitability demonstrates that there is a great activity in the motor cells of the spinal cord. It would seem from this research that strychnine stimulates both the sensory and motor tracts of the cord.

Since the convulsions of strychnine poisoning are of reflex origin,

if through any means sensory impulses are prevented from reaching the cord they do not occur; for instance, Poulsson found that after paralyzing the nerve-endings of the frog with cocaine no convulsions occurred after strychnine poisoning.

The probability of there being a stimulation of both sensory and motor systems receives some confirmation in the facts on one hand

FIG. 19.—Showing the effect of strychnine on the circulation before and during the convulsive period. The strychnine was injected at the point marked with an arrow; at C a convulsion occurred. Time marker indicates 2 seconds.

that there is an increased acuity of the special senses—vision and hearing—and on the other that centers in the medulla which are essentially motor in their character, such as the respiratory and the vasomotor centers, are excited by the drug; and, secondly, by the work of Hare, who found demonstrable histological changes in the anterior cornua.

After very large doses in the frog the period of convulsions is followed by one of complete paralysis; this is brought about through a paralytic effect upon the motor end plates similar to that produced by curare.

Circulation.—In full doses strychnine produces a rise of blood-pressure through a stimulant action upon the vasomotor center in the medulla. During the period of convulsion a further elevation of the blood-pressure is brought about by the violent contractions of the

muscles and by the accumulation of carbonic acid, the result of cessation of respiratory movement.

That the rise of blood-pressure caused by non-toxic doses of strychnine is of vascular origin is shown by the fact that after section of the spinal cord, thereby separating the vessels from their controlling nervous system, the elevation is either entirely lacking or very insignificant.

Our knowledge of the effect of strychnine on the heart is not absolute, but it is improbable that it exercises any marked stimulant effect upon this organ. The moderate dose seems to produce some

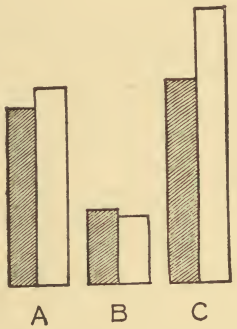

FIG. 20.—Diagram illustrating the effects of strychnine on respiration. The shaded columns represent the number of respirations per minute, the unshaded the total amount of air moved each minute. A is the normal, B after chloral had been given, and C after a subsequent dose of strychnine. Observe that the strychnine entirely overcame the depressant effect of the chloral and that the amount of air moved was increased more than the number of respirations, showing that strychnine increased the depth as well as the rate of the breathing.

slowing of the pulse, probably through a stimulation of the inhibitory center.

Respiration.—The respiratory center is also increased in its excitability by strychnine, but the effects are more marked in animals whose respirations have been reduced by poisons than in normal ones. The drug is unique among our respiratory stimulants in its power to overcome the effect of depressant poisons.

Absorption.—Strychnine is absorbed rapidly, whether taken by the mouth or administered hypodermically. The question whether it is absorbed through the stomach has been the subject of considerable research, which, however, is contradictory in the results. It is eliminated, also, comparatively rapidly, at least in part unchanged, but according to Plugge a portion of it is converted into strychnic acid.

Strychnine excites intestinal peristalsis, probably acting upon the ganglionic cells of the plexus of Auerbach. According to Langley and Magnus it causes rhythmical contractions of the intestinal muscles similar to those seen after atropine.

Therapeutics.—The physiological action of strychnine suggests its

use for the following purposes: (1) As a bitter tonic; (2) as a motor stimulant; (3) as a stimulant to the respiration; (4) as a stimulant to the vasomotor center.

As a bitter tonic strychnine is generally administered in the form of nux vomica; as the dose ordinarily employed for this purpose is too small to produce any physiological action from its absorption, there is practically no difference in its effect from that of the simple bitters (see page 242). Strychnine and nux vomica have been enormously used, and often in cases in which they can be of no possible benefit, as "general tonics." The term "general tonic" seems at times to be used to indicate a substance that may be administered when the doctor does not know what is the matter with the patient. The author feels that a drug as powerful in its effects upon the system as strychnine should not be administered unless the prescriber has a definite idea of what he hopes to accomplish with it.

Strychnine was originally introduced with the hope that through its powerful excitant action upon the motor system it would prove of value in cases of paralysis, but a moment's meditation will show that the conditions under which it can be of service for this purpose are very limited. For instance, in cases of hemiplegia following apoplexy, since the loss of power is due to lesions in the brain, it is very evident that strychnine can have no influence in restoring function. In those forms of paralysis in which there is destruction of the anterior cells of the cord, such as the acute poliomyelitis commonly known as infantile paralysis, it is evident that no drug can restore the destroyed nerve-cells, and strychnine, if used early, may do much harm by irritating the surrounding area of inflammation. Likewise, in cases of paralysis following inflammatory conditions of the motor nerves, it is manifest that the drug is of little value. Practically the only conditions in which strychnine is useful to relieve paralysis are in those forms which are due to the action of depressant poisons upon the spinal cord, and of these the only one of much importance is that which is occasionally seen as the result of chronic lead poisoning.

Attention may be further called to the possibility of evil effects from the use of strychnine in neurasthenia. This condition is essentially one of exhaustion, and, while stimulants may temporarily set aside certain symptoms, they do so at the expense of the reserve energy. It is an unfortunate misapplication of terms that strychnine has come to be regarded as a tonic; it is, in fact, a stimulant.

As a respiratory stimulant strychnine is probably our most reliable drug in the treatment of depressant poisonings such as opium, chloral hydrate, ether, and the like. In these states it should be given in full dose; as high as one-tenth of a grain may in extreme cases be administered hypodermically. It is also useful in certain respiratory diseases, especially in the chronic bronchitis of the aged and feeble, in which there is difficulty in expelling the bronchial secretions. Its value

in pneumonia is probably more through its influence upon the circulation than upon the respiration.

As a vasomotor stimulant strychnine is probably the most widely used of all drugs in the treatment of acute circulatory failures such as are seen in surgical shock, infectious fevers, and poisoning by depressant drugs. While in the normal animal, unless given in toxic doses, strychnine causes only a moderate rise in the blood-pressure, in many conditions of low tension it seems to produce much more powerful effects; thus Burnett has reported an increase of as much as forty millimeters in the human being from its use. Certain writers, because of the failure of strychnine to benefit the circulation in various experimental conditions, have condemned this use of the remedy. One cannot expect, however, that any stimulant will succeed under all conditions; if there is too large a dose of depressant poison in the blood to be overcome, or if as the result of morbid processes there is actual degeneration in the circulatory apparatus, it is not surprising that strychnine, as any other stimulant, will fail. I do not believe that the widespread confidence in this drug is altogether misplaced. In many of the instances in which it apparently failed to produce the desired result the fault has been due to too great timidity in its employment. One need hardly expect any effect on the circulation from doses of less than one-thirtieth of a grain administered hypodermically, and under ordinary circumstances the twentieth of a grain is a much better dose.

In connection with its effect upon the circulation may also be mentioned the use of strychnine in certain types of chronic heart disease, especially where there is myocardial changes. How it does good in these cases is, with our present knowledge of its effects, entirely inexplicable, but the clinical evidence of its beneficial action seems too strong to be lightly denied. I do not know of any criterion by which it is possible to foretell whether in an individual case the remedy is likely to prove useful, but it is certainly worthy of a trial in cases where digitalis has failed.

Strychnine has also been recommended in full dose for the relief of toxic amblyopia, especially that which is due to tobacco or alcohol. In chronic alcoholism it does good by antagonizing the effect of the alcohol upon the respiratory and vasomotor centers and spinal cord, and also by virtue of its local stimulant action upon the stomach.

HYDRASTIS.

Materia Medica.—The rhizome and roots of *Hydrastis canadensis,* an indigenous perennial, commonly known as Golden Seal. Hydrastis contains the alkaloid *berberine;* it owes its yellow color to this and probably also to other alkaloids, *canadine* and *xanthopuccine.* The most characteristic alkaloid is *hydrastine.* The latter occurs in brilliant four-sided prisms, inodorous and almost tasteless, but having a very bitter and somewhat acrid taste when in the form of a salt. Pure hydrastine and its salts can be obtained in the shops, but the hydrast*in*

of commerce is an impure body containing berberine, hydrast*ine*, and probably other more or less active alkaloids besides resin.

Official Preparations:

Fluidextractum Hydrastis .....½ to 1 fluidrachm (2–4 mils).
Glyceritum Hydrastis .....½ to 1 fluidrachm (2–4 mils).
Tinctura Hydrastis (20 per cent.).....1 to 2 fluidrachms (4–8 mils).
Hydrastina .....⅙ to ½ grain (0.01–0.03 Gm.).

Physiological Action.—The alkaloid *berberine* is almost inert save for its local action. In small doses it acts as a simple bitter, but in large quantities is irritant to the mucous membranes and also depressant to the central nervous system.

Hydrastine is a stimulant to the motor side of the spinal cord, producing, in the lower animals, violent convulsions with heightened reflex activity. In the frog, if the dose is sufficient, this is followed by a condition of paralysis which appears to be due to an action upon the peripheral motor nerves.

The respiration is at first hurried, but later becomes slow and shallow, and in the mammal, if death does not occur during convulsion, the fatal result is due to respiratory failure.

Concerning the effects upon the circulation our knowledge is not complete. When injected into a vein hydrastine causes a temporary fall in the blood-pressure, followed by a rise to a point generally above the norm. The rise in pressure, which is only moderate, is due chiefly to vascular constriction, but whether of central or peripheral origin cannot be decided from the present evidence. Concerning the effects upon the heart there is absolute contradiction between the results obtained by various investigators, some asserting that it increases the amplitude and power of the heart-beat, while others obtained no evidence of stimulation, but marked weakening of the organ. In moderate doses it has practically no effect upon the vagus, but large doses appear to paralyze the peripheral ends of this nerve.

According to the work of Kehrer, hydrastine increases the uterine tone and strength of contractions, and is capable of causing a tetanic condition of this organ, either when applied directly to the muscle of the uterus separated from the body or when administered to living animals. The same author found that berberine had little, if any, influence on the uterus. Whether this action of hydrastine is directly upon the muscle or upon contained ganglia is not known.

Therapeutics.—Hydrastis is popularly attributed with the power of exercising remarkable effects upon inflamed mucous membranes when applied locally. It has been used with asserted excellent results in chronic gastro-intestinal catarrhs, especially those due to alcoholic excesses. In the second stages of gonorrhœa, after the acute inflammation has been subdued, injections of hydrastin, or the fluidextract, suspended in mucilage, are often of service; ten to twenty minims of the fluidextract may be used to the ounce of fluid. It is also asserted by various specialists that in nasal, vaginal, and other catarrhs the

remedy is locally of great value. In dyspepsia it has been used as a stomachic stimulant, and has received especial praise in the vomiting of pregnancy.

It is also of service in mucous colitis, given by high injection in the strengths of about one tablespoonful of either the fluidextract or the glycerite to the quart of water.

Hydrastis has been used to a considerable extent, with asserted good results, in uterine diseases, as fibroids, menorrhagia, and various forms of hemorrhage from the womb. For internal or general medication the alkaloid or its salts is to be preferred to preparations of the whole drug. As anti-hemorrhagic or ecbolic, *hydrastine* may be used in doses of from one-sixth to one-half grain (0.01–0.03 Gm.).

HYDRASTININE HYDROCHLORIDE.

Hydrastinine is an artificial alkaloid first produced by Martin Fruend by the oxidation of hydrastine but now also made synthetically from berberine and from safrol. The hydrochloride is a light yellow crystalline powder, somewhat deliquescent, odorless, having a bitter saline taste, soluble in 0.3 part of water and three parts alcohol.

Hydrastininæ Hydrochloridum.....¾ to 1½ grains (0.05–0.1 Gm.).

Physiological Action.—Hydrastinine differs markedly from hydrastine in its effects, especially in that it is not stimulant to the motor side of the spinal cord, but in large doses is a depressant to the whole motor tract, lessening the irritability of the psychomotor area, of the spinal centers, and probably also of the peripheral motor nerves.

The influence of hydrastinine upon the circulation is more positive than that of the natural alkaloid, and all observers are agreed that it causes a rise in the blood-pressure. This appears to be due partly to a stimulant influence upon the heart muscle and partly to a constriction of the arterioles due to a direct action upon their muscular coats.

Upon the uterus the action of hydrastinine is similar in kind, but more marked in degree, to that of hydrastine. Keher finds that it is but little less powerful in its effects than the best preparations of ergot.

Therapeutics.—Hydrastinine is used in medicine chiefly in the treatment of uterine conditions such as menorrhagia, dysmenorrhœa, and even endometritis. It has also been employed to a slight extent as a general circulatory stimulant, but there is at present not sufficient clinical evidence to justify a conclusion as to its value.

Its effects upon the motor area of the brain suggest its use in epilepsy, but we know of no direct evidence of its utility in this disease.

COTARNINE.

This is an artificial alkaloid which is an oxidation product of narcotine prepared by prolonged boiling of this alkaloid with undiluted nitric acid. The hydrochloride is official. It is a yellow deliquescent

crystalline powder, freely soluble in either water or alcohol. The dose is from ½ to 2 grains (0.03–0.13 Gm.).

Chemically cotarnine is closely related to hydrastinine, and may be regarded as a methoxy-hydrastinine.

Therapeutics.—The only important effect of cotarnine upon the system is its stimulating action upon the uterus. It is a direct stimulant to the uterine muscle, and if used in a large quantity may cause a clonic spasm of this organ.

Cotarnine differs from hydrastinine in that it is not a stimulant to the circulation. Although the heart may be somewhat strengthened in the force of its beat there is a sufficient reduction in the number of cardiac contractions to compensate for this fact, and there is practically no constriction to the blood-vessels. After small doses the blood-pressure is unaffected, and large quantities tend to lower rather than increase.

Cotarnine has been used with success for the control of hemorrhages from the uterus, more frequently in those forms which are not due to the accidents of pregnancy, that is in the menorrhagias. It has also been widely employed to check bleeding from other portions of the body, and although many have reported cessation of the hemorrhage after its use, it is doubtful whether the drug had anything to do with the result. As stated above, it is not a vasoconstrictor, and the experiments of Laidlaw seem to demonstrate that it has no influence on the rapidity of coagulation.

ERGOT (U. S.).

Materia Medica.—Ergot is a blackish body, one to two inches in length, irregularly cylindrical, grooved along one side, and very generally curved; it is composed of very thick-walled microscopic cells, containing oil-drops but no starch. As was first demonstrated by Tulasne,* ergot is the sclerotium of the *Claviceps purpurea* (Tulasne) which infests the grain of *Secale cereale,* or rye.

Ergot is a complex body, containing at least two characteristic alkaloids and a number of amines which are found elsewhere, especially as the result of putrefactive processes in proteid bodies. The characteristic alkaloids are two substances, closely allied chemically, known as ergotinine and hydroergotinine (ergotoxin). Ergotinine, which is a crystalline base, is practically inert. The second alkaloid is an amorphous body which differs in its chemical composition from ergotinine in that it possesses one molecule more of water. It was discovered almost simultaneously by Barber and Walpole and by Kraft. The first-named authors suggested for its name the term ergotoxin, but Kraft used the term of hydroergotinine to show its relation to the

* Among the lowest of vegetable organisms, and distinguished from other plants by the absence of chlorophyll, are the fungi. There are in most cases two distinct states or stages in the life of a fungus: in the first of these, the vegetat-

older alkaloid. Hydroergotinine appears to exist in ergot in combination with a resinous acid. The substance described by Kobert as the active principle of ergot under the name of cornutine does not appear to exist in ergot as such, but to be a product formed by the processes used for its extraction. The resinous bodies which have been described under the name of sphacelinic acid and sphacelotoxin seem to be inert, such action as has been ascribed to them being due to contamination with the active alkaloid. Besides these peculiar alkaloids and a number of inert substances, ergot contains several active amines which have been found also in various putrescent proteins; the most important of these are parahydroxy-phenylethylamine (tyramine) and beta-iminazolylethylamine (histamine).

The characteristic active alkaloid of ergot is insoluble in water and most of the salts which it forms are but sparingly soluble. It is evident, therefore, that an aqueous preparation of ergot cannot entirely represent the crude drug. Of the official preparations the only one that represents the entire activity of ergot is the fluidextract. Most of the proprietary preparations on the market, especially those intended for hypodermic administration, being aqueous extracts, do not possess the full therapeutic virtues of the fluidextract. Both the crude ergot and the fluidextract deteriorate rapidly with age, especially if exposed to the air. Because of this fact the majority of samples of fluidextract of ergot as obtained in the retail market are physiologically very feeble.

Official Preparations:

Extractum Ergotæ.....3 to 5 grains (0.2–0.3 Gm.).
Fluidextractum Ergotæ.....½ to 2 fluidrachms (2–7 mils).

Physiological Action.—The effects of ergot are a combination of the actions of its active principles. Ergotoxin is a stimulant to unstriped muscles including the heart, the arteries, the intestines, the uterus, etc. Tyramine is a stimulant to the endings of the sympathetic nerves and closely resembles epinephrine in its actions. Histamine appears to be like ergotoxin, a stimulant to involuntary muscles, but

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ing period, it exists as a *mycelium*, a usually filamentous mass of flocculus, whose sole function is to grow and increase; in the second stage the *thallus*, or ordinary fungus or mushroom, is formed, and to it is assigned the function of developing reproductive bodies, after whose maturation it perishes. Between these stages there is in some fungi an intermediate one, in which the plant exists as a *sclerotium*. The genus Claviceps comprises a number of parasitic fungi, which develop in the pistils of the various species of Gramineæ. The first appearance of the ergot is in the flower of the rye, at the base of whose pistil arises a minute flocculent mass of mycelial filaments. These filaments, continually growing and invading all parts of the tissue of the pistil, at last form of it an irregular whitish body, at the base of which after a time appears a dark-colored body, the sclerotium, which continues to grow, lifting up the diseased and withering mass formed out of the original pistil, and finally developing into a perfect ergot.

has a specific action upon the vasomotor center whereby it dilates instead of contracts the blood-vessels. The action of ergotoxin is slow and prolonged, that of the amines comparatively prompt and fleeting. It is evident that the effects of any individual sample of ergot will vary more or less according to the relative amount of these three principles. Ergotoxin, which is the most characteristic, and in my opinion the most desirable constituent of ergot, is the one which is most frequently lacking. This is for two reasons. In the first place it is almost insoluble in water and therefore cannot be present in any large quantity in aqueous preparations of the crude drug. In the second place it is an easily oxidizable substance, being readily converted into inert ergotinine. The account given below of the physiological action of ergot represents that of an alcoholic preparation made from a good quality of drug and one, therefore, in which the ergotoxin is the dominant principle.

Circulation.—The intravenous injection of an active preparation of ergot produces a marked rise in the blood-pressure, which, under certain circumstances, notably when the injected dose is large, is preceded by a temporary fall. With proper doses the pressure may remain above normal for a period of several hours. If the dose be too large, however, it falls in about ten to fifteen minutes to a point slightly below the norm. If a second dose be then administered there occurs a temporary rise in the pressure, but it falls again in a few minutes to a point lower than that at which it was injected. Accompanying the rise of pressure there is a marked slowing of the pulse and an increase in the size of the wave.

After very large toxic doses the lowering of the blood-pressure may be extreme. It is worthy of note that in the pulmonary artery the primary rise of blood-pressure after large doses is not succeeded by a fall, so that when very large quantities are given the carotid and pulmonary pressures tend to approach each other.

Although certain of the older investigators assert that the rise of blood-pressure caused by ergot is prevented by section of the spinal cord, my own investigations, as well as those of most of the other recent authorities, show that such is not the case; indeed, it would seem that after destruction of the vasomotor center the elevation of the pressure is even greater than in the normal animal. The increased pressure is due, at least in part, to a constriction of the blood-vessels, probably through an action directly upon the muscular coats of the arteries, especially in the abdominal area. In the vessels of the limb there is sometimes a contraction, but in other experiments these vessels have dilated passively, owing to the greatly increased pressure.*

The slowing of the pulse is due to stimulation of the cardio-inhibitory centers, since it does not occur after section of the vagi. Whether this is a direct action of the drug or whether it is secondary

*Dale describes a remarkable condition in the cat following the injection of large doses of ergotoxin, in which epinephrin causes a fall instead of the customary rise in blood-pressure.

to the rise in blood-pressure is as yet uncertain. The increase in the size of the heart-beat seen after the injection of ergot is the result not merely of the slowing of the pulse but also of a direct stimulant influence upon the heart muscle.

A remarkable effect of ergot is its mortifying action in certain peripheral portions of the body. It is seen most characteristically in the comb and wattles of the rooster, but has occurred not infrequently in the tips of the ears of swine and has even been noted in the fingers of human beings as the result of accidental poisoning through eating smutted rye. This dry gangrene is due to the formation of a hyaline plug in the peripheral arteries, shutting off the circulation. The occlusion of the arteries was formerly attributed to a violent spasm of the blood-vessels, but it is more probable that an irritant effect upon the internal coat of the artery leads to the formation of the obstructing coagulum.

Uterus.—In moderate quantities ergot causes a marked increase in the extent of the rhythmical contractions of the uterus, with also an increase in muscle tone. After large doses the latter effect is so marked that it throws the uterus into a violent tetanic spasm, with almost complete obliteration of the waves of contraction.

This action upon the uterus appears to be the result of a combination of several factors, the various principles which have been so far isolated having somewhat different actions. As is pointed out in more detail in the article on epinephrine (see page 222), stimulation of the peripheral ends of the hypogastric nerve, which is the sympathetic supply to the uterus, will cause different results in varying species of animals and in varying conditions, and drugs acting on this nerve may provoke antagonistic effects. Para-hydroxy phenylethylamine, like epinephrine, stimulates the peripheral ends of the hypogastric nerve and will, therefore, cause contraction in the pregnant cat's uterus, but relaxation in the nulliparous cat, either when injected internally or applied directly to the isolated organ. Betaiminazolylethylamine seems to be a direct stimulant to the uterine muscle, tending especially to cause increase in tone and spasmodic contraction. The alkaloid hydroergotinine has comparatively little action upon the isolated uterine muscle, separated from the nervous system, but in the intact animal increases both the muscle tone and the vigor of contraction.

It is evident that the effect of a given sample of ergot upon the uterus will depend upon the predominance of one or other of these principles. As in a fresh preparation, of good quality of ergot, the dominant principle is the hydroergotinine, the effects will be, either in pregnant or non-pregnant, an increase in the vigor of contraction and, after large doses, also in muscular tone.

Unstriped Muscle.—The action of ergot upon the circulatory and uterine muscles is part of a wide-spread action upon all involuntary muscle-fiber. Meltzer and Auer have shown that it increases the tone

and peristalsis of the stomach and intestines, and Dale that it excites the muscles of the bladder, the sphincter pupillæ, and the erector pili.

Therapeutic Uses.—As a stimulant to the circulation ergot is especially used in the treatment of chronic congestions; thus it is often of value in serous diarrhœas, colitis, and diabetes insipidus. Da Costa has used it with asserted good results in enlargement of the spleen from various causes, even leukæmia. It has also been employed with asserted benefit to relieve pulmonic congestion in the early stages of pneumonia and in the pulmonic hyperæmia seen in the latter stages of typhoid fever. As a stimulant in acute circulatory failure its absorption through the ordinary channels is so slow that it is generally not valuable as a remedy. Osborne, however, asserts that injected intramuscularly it is of extreme value in surgical shock and similar forms of vasomotor paresis.

Owing to the power that ergot possesses of intensifying labor-pains, it has long been used in uterine inertia during parturition. Indeed, it was for this purpose that the drug was first employed in medicine, and thereby acquired the name of *pulvis parturiens*. If ergot be given in very small doses during labor, the natural pains are simply intensified; but if the dose be large enough to have a decided effect, their character is altered: they become not only more severe, but much more prolonged than normal, and finally the intervals of relaxation appear to be completely abolished and the intermittent expulsive efforts are changed into one violent, continuous strain. It is evident that, if the resistance be sufficiently great, this may endanger the safety both of the mother and of the child. The dangers to the mother are twofold: there is a possibility of the uterus rupturing itself by its efforts; and, when the head comes down upon the perineum, if the soft parts be rigid there is a very strong probability that they will be lacerated. The danger of uterine rupture is, we think, a remote one; for although several alleged cases have been recorded, yet in very few is the accident clearly traceable to the asserted cause. The fatal character of the accident is such, however, that the possibility of its occurrence should always prevent the reckless use of the drug.

The improper use of ergot is even more serious in its effects upon the child than upon the mother. During a violent uterine contraction the passage of the blood from the placenta to the child must be interfered with, or, in other words, the respiration of the fœtus is temporarily stopped, so that its life depends upon the aëration of the blood during the intervals. If the latter be very much shortened, the life of the child is greatly imperilled; and if they be abolished, it must be destroyed, unless delivery occurs in a very few moments. These considerations are, we think, sufficient, without further discussion, to show the imperativeness of the rule *never* to give ergot in uterine inertia when there is much *resistance,* either in the bony or in the soft parts of the mother. In primiparæ such resistance is always to be looked for, and its degree often difficult to judge of beforehand; and in such women ergot should not be used for the purposes of expulsion.

Even under the most favorable circumstances—when the woman has previously borne children, when the bony pelvis is capacious, and the soft parts are relaxed and dilatable—its use should be entered upon with caution; and if the accoucheur be skilful in the application of instruments, cases must be rare in which the latter are not preferable to the ecbolic.

In women of lax fiber, with roomy pelves, ergot may be cautiously used in uterine inertia if instruments are not at hand, or if they are objected to, or if the obstetrician is timid in their application.

At the close of parturition, ergot is very commonly employed to prevent postpartum hemorrhage; and in this case there is no objection to its use, and the remedy is invaluable. But, as it requires at least thirty minutes for its action when given by the mouth, ergot exhibited in this way cannot be relied upon to arrest flooding when it has already set in. To prevent the occurrence of the latter, it is an excellent rule to give a full dose of the ecbolic when the child's head is well down upon the perineum and beginning to emerge at the vulva. The obstetrician should remember, however, that much of the ergot upon the market is practically inert and therefore not rely on the drug to the exclusion of other modes of treating post-partum hemorrhage.

For the induction of premature labor ergot has been and still is to some extent used; but it is uncertain in its action, and offers no advantages over instrumental methods.

The success of ergot in arresting hemorrhage after labor soon led to its use in uterine hemorrhages in other than parturient or pregnant women. Thus it has been employed with more or less success in menorrhagia and metrorrhagia.

From its value in uterine hemorrhages it has also been employed to a considerable extent in internal hemorrhage. It is not evident, however, in what way it can be beneficial in hemorrhages other than from the uterus. It must be remembered that any substance which leads to a general vasoconstriction increases the force of the circulation. The increased pressure tends to dislodge any clot which may be formed at the bleeding point. Therefore those drugs which narrow the lumen of the vessels must incline to continue rather than check internal hemorrhages.

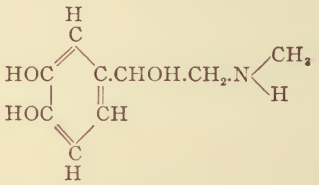
In colliquative night-sweats due to relaxation of the blood-vessels ergot is a most efficient remedy.

SUPRARENAL CAPSULE.

Materia Medica.—The suprarenal glands are two small bodies which are located in all mammals just above the kidney. For medical purposes they are generally obtained from the sheep or from the ox. The gland freed from fat, dried, and powdered is recognized by the United States Pharmacopœia. It occurs as a yellowish, brown amorphous powder with a faint, somewhat meaty, odor, yielding its activity to, although not completely soluble in, water. Histologically the supra-

renal gland consists of two portions—a medullary and a cortical area. The cortical layer seems to have for its function the destruction of certain toxic substances. In the medullary portion there is found an alkaloid-like substance, epinephrine.* This has finally been determined definitely to be an ortho-dioxyphenyl-ethanol-methyl-amine.

There seems to be little room for doubt that this alkaloid is part of a true secretion, and that the activity of the suprarenal gland is governed through the splanchnic nerves.



Epinephrine.

Synthetic epinephrine was first prepared by Stolz. As first prepared synthetic epinephrine differed from the natural alkaloid in being optically inert and physiologically much less active. In 1908 Flacher succeeded in separating the optically inert synthetic alkaloid into two portions, a dextro- and a lævorotary substance. Abderhalden and Mueller have shown that the lævorotary form is some fifteen times as active physiologically as the dextrorotary form.

Suprarenalum Siccum....3 to 5 grains (0.2–0.3 Gm.).

Physiological Action.—Epinephrine excites to higher functional activity the organs supplied through the sympathetic nerve system. The action seems to be upon the peripheral endings of the nerve. This action upon the nervous system will manifestly give rise to a large variety of alterations in the bodily functions and the symptoms will be dissimilar in various animals, according to the different functions of the sympathetic nervous system. A striking example of this is found in the cat's uterus. In the nulliparous animal stimulation of the hypogastric nerve checks muscular contractions, while in the pregnant animal stimulation of the same nerve augments muscle contractions. These antagonistic effects are also caused by epinephrine. While the action of this remedy is wide-spread, the most important effects are those upon the circulation.

Circulation.—The injection of any preparation of epinephrine into

* This active principle has been placed upon the market under a variety of trade names, such as adrenalin, suprarenin, suprarenalin, adrin, supracapsulin, etc., etc. While in medical literature the substance is commonly referred to by one or other of its trade names, it seems wiser to apply to it a name in which there is no ownership, and the name which was given it by the man who more than any one other man was responsible for its isolation.

a vein brings about an extraordinary rise in the blood-pressure, accompanied during the period of high pressure with a marked slowing of the pulse, the effects lasting from one to ten minutes, according to the dose and various circumstances. After section of the vagi, as well as in the isolated heart, the rate is increased rather than slowed. Whether or not the excitation of the cardio-inhibitory mechanism is due to a direct action of the drug or simply the reflex result of the high blood-pressure is as yet open to difference of opinion. The elevation of the pressure is due chiefly to a violent contraction of the arterials, although at the same time there is a stimulation of the heart. After considerable doses, despite the stimulant effect of the drug upon the heart, the resistance offered by the arteries is so enormously increased that the heart is unable to overcome it and acute dilatation may ensue. All of

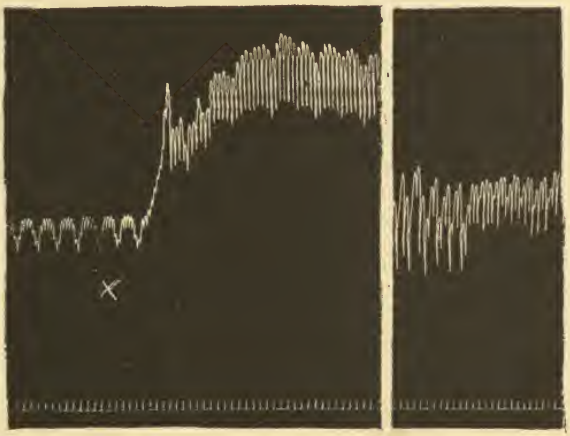


FIG. 21.—The effect of epinephrine on the blood-pressure. The epinephrine was injected at X; the second piece of the tracing shows the pressure two minutes after the injection. Note the transiency of the rise, also that the increase in pressure precedes the slowing of the pulse.

the arteries of the body, with a possible exception of the coronary, appear to share in the stimulation produced by the drug; the statements sometimes made that the pulmonary arteries are not constricted by epinephrine have been disproven by Wiggers and by myself.

The repeated injections of epinephrine produce in the rabbit sclerosis of the aorta and myocardial degenerations. These changes in the blood-vessels appear to be dependent upon a specific irritant action on the intima, although there is reason to believe that the great rise in blood-pressure is an exciting factor. It has been shown by Schrank that the simultaneous injection of certain oils protects, at least to a certain extent, the animal against these arterial degenerations. Falk has confirmed this observation, and states that any substance which produces a leucocytosis will prevent the arterial changes. What bearing these facts have upon human medicine is at present not clear. It is a striking fact that similar changes are not produced in the dog.

Bronchi.—When injected into the normal animal epinephrine causes little if any change in the caliber of the bronchi, but if for any reason the bronchial muscles be restricted it causes an immediate relaxation. This effect is generally explained on the theory of the existence of an inhibitory center for the bronchi belonging to the sympathetic system, whose terminals would be stimulated by epinephrine.

Uterus.—As mentioned above, the effects of epinephrine are the same as those of stimulation of the sympathetic nerve, and whether contraction or relaxation follows its administration depends upon the specie of animal. While the function of this nerve has not been definitely proven in the human being, the observations of Neu would seem to demonstrate that the effects of epinephrine in the woman is always predominatingly motor.

Other results of the action of adrenalin upon the sympathetic system are dilatation of the pupil, inhibition of peristaltic movements of the alimentary tract, increase in the secretion of the salivary glands.

Nutrition.—The injection of epinephrine gives rise to hyperglycæmia and glycosuria. This seems to be due to an effect upon the pancreas, since Hurter and Richards have found degenerations in the island of Langerhans, and, according to Frugoni, the simultaneous injection of pancreatic extract prevents the epinephrine glycosuria. It has further been shown that epinephrine prevents the increase of pancreatic secretion which is caused by secretin.

Elimination.—The rise in blood-pressure which is caused by the intravenous injection of preparations of the suprarenal gland is extraordinarily fugacious, lasting, after small doses, not more than one minute, and, even after large quantities, rarely more than five. Moreover, when the remedy is given hypodermically it requires relatively enormous quantities, nearly one hundred times the intravenous dose, to elevate the blood-pressure, and when given by the mouth its characteristic effects upon the circulation are entirely absent. The lack of duration in the effects of epinephrine have been attributed variously to its rapid disappearance from the blood and to an excitation of some antagonistic mechanism. That its evanescence is not to be explained on the ground of elimination through the kidney is shown by the fact that even after ligation of the renal arteries the action is very transitory. Tatum believes that there is some substance in the arterial walls which is capable of destroying the physiological activity of adrenalin. Meltzer and Auer believe that the transitoriness of the effects is due to an excitation of some antagonistic influence in the sympathetic ganglia, but the fact that repeated doses of the drug produce practically the same degree of effect and that by continuous slow injection a prolonged effect may be produced, argue against this view.

Therapeutic Uses.—Because of the extreme fugaciousness of its action epinephrine is not of great practical importance as a general circulatory stimulant. In cases, however, of sudden vasomotor failure, such especially as are seen in the surgical amphitheater, by keeping the

patient alive until slower and more persistent drugs have time to exercise their influence, epinephrine may prove a very valuable remedy. The most serious drawback to this employment of the drug, however, is the fact that it is relatively powerless when injected subcutaneously. The intravenous injection cannot always be safely performed instantaneously; the preparation of the patient for the intravenous injection may occupy nearly as long a period of time as the action of the drug is likely to last. It is probable, however, that if it is injected deeply into the muscle substance instead of into the subcutaneous tissue it is absorbed with sufficient rapidity to exercise its characteristic influence upon the circulation. With the idea of prolonging the duration of its effects it has been suggested that very dilute solutions of the drug in physiological salt solution should be injected continuously, thus obtaining the beneficial effects of saline infusion as well as of epinephrine stimulation. The dose as an internal remedy is from 5 to 15 minims (0.3–1.0 mil) of the 1 to 1000 solution.

The most frequent employment of this drug is as a local vasoconstrictor. It has been widely employed in the treatment of acute inflammations of mucous membranes such as conjunctivitis, rhinitis, and the like. Under these conditions it causes a disappearance of the congestion through its constricting effects upon the blood-vessels, but, as pointed out on page 76, it is at least questionable whether constriction of blood-vessels is an end to be striven for in acute inflammations. In chronic congestions of mucous membranes as in hay fever its use is more logical than in acute inflammatory conditions, and is often the source of much comfort to the patient. As a local styptic, especially when the hemorrhage is from the smaller vessels, it is one of the most valuable of the remedies we possess. It is not only employed to check bleeding, but also to prevent hemorrhage during operations on the nose, throat, or eye. In order that it may act efficiently as a hæmostatic it is essential that it be brought in intimate contact with the ruptured blood-vessels and in relatively concentrated solution; in cases where the bleeding is profuse it is sometimes impossible to bring it in contact with the bleeding point, as it is washed away so rapidly by the blood and, therefore, it may fail. Especially is this the case in hemorrhage from those mucous membranes where it cannot be directly applied, as, for instance, in the stomach. As a remedy in internal hemorrhage where we must trust to its reaching the bleeding point through the means of the circulation its value is extremely problematical. In uterine hemorrhages, however, especially those after labor, it may prove a remedy of great value by virtue of its stimulating the uterine muscle, which checks the bleeding, and at the same time, by this vasomotor stimulant effect tends to counteract the circulatory failure which may have occurred as the result of the loss of blood.

A number of years ago, Cohen highly recommended the use of the suprarenal gland by oral administration in the treatment of asthma. His method, however, did not attract a large number of followers, but more recently the active principle has been used by intramuscular

injection in the treatment of asthmatic paroxysms. In many cases the relief is very marked and almost instantaneous. While in some cases the patient may remain free from his dyspnœa for the remainder of the night, often the relief is only temporary, the paroxysm returning within an hour, or less.

While not of itself in any degree anæsthetic, it often greatly enhances the action of the local anæsthetic, such as cocaine, because by its violent constriction of the blood-vessels it limits the action of these remedies more narrowly to the point of application.

Suprarenal capsule is also useful as a symptomatic remedy in that condition known as Addison's disease, which depends upon a destruction, usually cancerous, of the suprarenal gland. For this purpose the crude drug should always be given the preference to the blood-pressure raising principle.

HYPOPHYSIS.

The hypophysis cerebri or pituitary body is a small structure resting in the *sella turcica* at the base of the skull. It consists of three parts, an anterior lobe, which is glandular in structure, a narrow intermediate part, and a posterior lobe, often known as the infundibulum, which is composed chiefly of nervous tissue. The U. S. Pharmacopœia recognizes the dried whole organ. One grain of the dried gland is equivalent to approximately six of the fresh.

Official Preparations:

Hypophysis Sicca .....½ to 1 grain (0.03–0.06 Gm.).
Liquor Hypophysis .....10 to 20 minims (0.6–1.3 mils).

Physiological Action.—The anterior lobe of the hypophysis has some important, but not well understood, influence upon the bodily metabolism, especially of the osseous system. In cases of acromegaly and gigantism there is frequently found tumor of the hypophysis, but whether overgrowth is due to the destruction of the gland or to an increase in its secretion is as yet unsettled. The continued administration of hypophysis leads to a marked increase in the elimination not only of nitrogen but also of phosphates and of calcium. The losses in the latter substance have been generally taken to betoken an increased catabolism of bony tissue. In this connection it is interesting to note that Ott and Scott have found that the gland will temporarily, at least, relieve the convulsions caused by parathyroidectomy, which many believe are due to a deficiency of lime in the blood.

The posterior portion of the hypophysis, when introduced into the circulation, has three distinct actions. It stimulates unstriped muscle, increases the flow of urine, and increases the flow of milk.

Circulation.—When a solution of infundibulum is injected into a vein it produces an extraordinary rise of the blood-pressure, lasting for from 10 to 30 minutes or more. If the second dose be administered within a period of a couple of hours the rise which occurs is usually of lesser extent and may be followed by a fall below the normal. After

each subsequent injection the rise becomes less marked and the secondary fall greater, until eventually the drug causes a lowering of the pressure. During the period of high blood-pressure there is marked slowing of the pulse, but this appears to be simply the reflex cardiac inhibition caused by hypertension. The rise in blood-pressure is due to vascular constriction, the result of direct action upon the muscular coats of the arteries. The heart muscle does not seem to share in the stimulating influence of the drug; indeed, some authorities claim that it is even depressed.

The cause of the secondary lowering of the blood-pressure after repeated doses is as yet a mooted point. Some believe that there is present in the gland a second depressant substance which is less rapidly eliminated than the pressor substance, and therefore on repeated dose tends to overcome the stimulating action, while others maintain that it is due to exhaustion of the heart pumping against high arterial resistance. Of the other muscular organs affected by this drug, the most important from a medical standpoint are the intestines and uterus. In sufficient dose it will throw the uterus into prolonged spasmodic contractions, but in smaller quantity may increase the force of the rhythmical contractions without disturbing their rhythm. It is capable of causing abortion.

Secretion.—So far as known, the only blood-vessels in the body which are not contracted by pituitary are those of the kidney, which after proper doses may be even dilated. The local dilatation of the renal circulation, however, seems to be the result of the increased functional activity of the kidney and consequent demand for blood rather than the cause of the diuresis; in other words, the increase in the quantity of urine is due to a direct stimulation of the renal epithelium.

The injection of pituitary extract is followed by an immediate and marked increase in the flow of milk. Not only is the quantity augmented, but there is also an increase in the percentage of fat in the secretion. This stimulation of lacteal secretion lasts only a short time, but can be called forth again by a second injection. Whether the twenty-four hours quantity of milk can be increased by repeated doses does not appear as yet to have been determined, but Hill and Simpson find that the percentage of fat may remain above the normal for twenty-four hours.

Therapeutic Uses.—The precise clinical value of pituitary as a circulatory stimulant has not been established. In acute vasomotor failure, as surgical shock or hemorrhage, theoretically it should be of great value, and there are some scanty clinical reports to substantiate this conclusion. Although in the pharmacological laboratory the repeated dose fails to produce the same rise in blood-pressure, Musser has found it possible through oral administration of the gland to maintain a pressure 10 or 20 millimeters above the normal for several weeks. These results would certainly merit at least a trial of the drug in the circulatory failure as seen in the latter stages of infectious diseases. There is

likewise but scanty clinical testimony to its value as a diuretic, but it would seem to be worthy of a trial in the same class of cases in which caffeine is useful. As a galactagogue it is sometimes of service for the purpose of establishing secretion after labor, but in cases of permanent scantiness of milk it does not appear to be capable of maintaining the secretion.

The most important clinical use of pituitary extract at present is as a uterine stimulant, either in the treatment of menorrhagia or for the relief of uterine inertia during labor. In the latter condition, because it is less liable to cause tetany of the uterus, it is a safer drug than ergot, at least as far as the child is concerned. On the other hand, it is not free from danger for the mother and should not be used indiscriminately; Quigley has reported three cases of uterine rupture from its injudicious use, and it should be employed only with the same precautions which have been quoted for ergot. For the control of postpartum hemorrhage it is inferior to ergot in the relatively short duration of its effects.

Hypophysis has been also clinically recommended to overcome paralysis of the intestines after abdominal operations, in the treatment of exophthalmic goitre, to increase the coagulability of the blood for the control of hemorrhage, especially in nose and throat operations, and in asthma.

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DRUGS WHICH LOWER THE BLOOD-PRESSURE.

Drugs may lower the blood-pressure either by lessening the functional activity of the heart or by causing a widening of the blood-vessels. Changes in the output of the heart may be brought about through decreases in its muscular power or reduction in the number of the beats. There is considerable difference in the field of clinical utility between a drug which lessens heart action and one which causes dilatation of the blood-vessels, and we may conveniently divide the

agents used for reduction of excessive pressure into two groups—those which act upon the heart, and those which affect the vasomotor system. The drugs which are used clinically for lessening the heart action are veratrum and aconite. The only remedies whose vaso-dilating action is of practical moment are those which liberate the nitrite ion in the system.

It was formerly believed that aconite and veratrum lowered blood-pressure largely through a direct influence upon the heart muscle, and they were therefore classed as cardiac depressants, but, as we shall see, recent investigation has shown that they are not, properly speaking, cardiac depressants, since they do not materially weaken the potential force of the heart muscle. They act largely by stimulating inhibition, and in this regard may be compared in their clinical value to digitalis.

The lowering of the blood-pressure, *per se,* is an end to be striven for less frequently than has been taught.

VERATRUM.

Materia Medica.—Veratrum is the rhizome and rootlets of the *Veratrum viride,* commonly known as the American hellebore, or of the *Veratrum album.* Botanists are not agreed as to whether these plants are distinct species or merely varieties of the same species. The *V. album* is found in Europe, while the *V. viride* is a common weed in damp and woody grounds of the northeastern United States. Practically all of the drug used is derived from the American species.

Although a number of alkaloids have been isolated, it is still doubtful what is its most important active principle. The alkaloids which have so far been discovered are jervine, rubijervine, pseudojervine, cevadine, and protoveratrine. The first three named are so feeble physiologically that they cannot play any great rôle in the action of the drug, and cevadine (veratrine) is found only in such minute quantities in the *Veratrum viride,* and apparently not at all in the *V. album,* that it is impossible to attribute the virtues of these plants to it. Protoveratrine seems at present to be the most important substance, but it is probable that there still remains some undiscovered principle.

The official portion is the rhizome and roots, which appear in the market usually in pieces, but when entire the rhizome is one to three inches in length and a little less than an inch in diameter, tapering to a very obtuse or truncated end, of a dark brown color, and bears numerous yellow rootlets several inches in length, or else the marks of their removal. It has a bitter, acrid taste, is inodorous, but its powder, when snuffed, produces violent sneezing.

Official Preparations:

Fluidextractum Veratri .....1 to 3 minims (0.06–0.2 mil).
Tinctura Veratri (10 per cent.).....10 to 30 minims (0.6–2.0 mils).

Physiological Action.—Locally veratrum is irritant to mucous membrane, acting as a violent sternutatory when inhaled, and as an

emetic if swallowed in sufficient quantity. It is probable, however, that its emetic action is partly due to an effect upon the vomiting center. In discussing the general action of this plant, we must make sharp distinction between the effect of the various alkaloids. It was until very recently believed that the activity of the plant was due chiefly to the alkaloids jervine and rubijervine, but the latter has been shown to be a comparatively feeble poison, and probably plays no rôle in the effect of the whole plant.

Jervine is a depressant to the respiratory center, to the vasomotor center, and to the heart muscle. Rubijervine stimulates the cardio-inhibitory centers, but appears to depress the respiratory center. This effect upon the cardiac muscle is very slight.

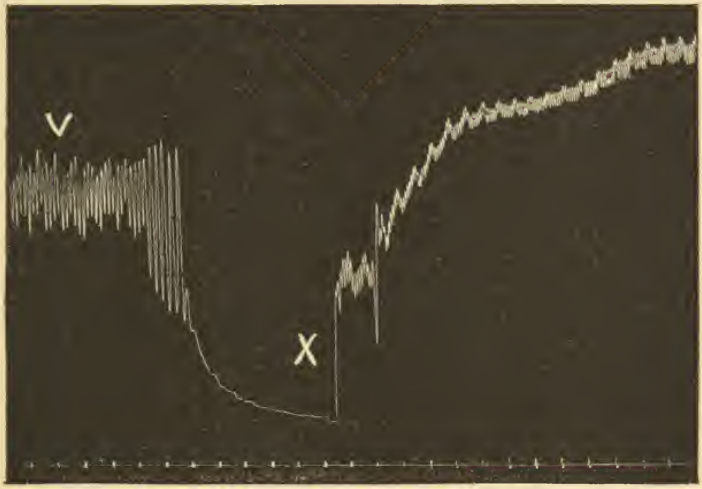

FIG. 22.—The effect of veratrum on the circulation. This shows that the fall of pressure caused by veratrum is due solely to the slowing of the pulse, because the pressure rises above normal after section of the pneumogastric nerves. V, Injection of veratrum. X, Division of both pneumogastric nerves. Time marker indicates 2 seconds.

Protoveratrine is by far the most active substance found in veratrum, the fatal dose being about 0.1 milligramme per kilo, according to Eden. Moderate doses produce a marked slowing in the pulse-rate with fall in the blood-pressure, and after very large doses there is a secondary increase in the pulse-rate with a rise of the pressure. Neither the slowing of the pulse nor the fall in the blood-pressure occurs after section of the two pneumogastric nerves.

I have found that the effects of veratrum itself are very similar to protoveratrine, although the effects of the plant seem to be slightly modified by the other alkaloids. In the normal dog there is a marked fall in the pulse-rate and blood-pressure, both of which effects are abolished by section of the vagi. If the pneumogastric nerves are cut previous to the administration of the drug, there is generally a rise in blood-pressure and the pulse-rate remains unchanged. In a few in-

stances, however, a slight lowering of the pressure has been noted instead of the common elevation. The fall of the blood-pressure may therefore be regarded as due solely to the marked slowing of the pulse, the result of stimulating the inhibitory center.

After toxic doses there is an increase in the pulse-rate beyond the norm, due to a paralysis of the peripheral ends of the vagus. The large dose also induces a fall of the blood-pressure—even when the pulse is rapid—probably by lessening the force of the heart, although it is possible that there may also be a vasomotor paresis.

Veratrum, in large doses, acts as a powerful depressant to the respiratory center, death after fatal quantities usually being due to a failure of this function. In sufficient dose it also acts upon the motor side of the spinal cord as a direct depressant, producing loss of reflexes.

Therapeutic Uses.—The eclectic practitioners have, under the belief that veratrum possesses some mysterious antiphlogistic properties, introduced its use in the treatment of pneumonia, peritonitis, and other sthenic inflammations. The regular medical profession for a while continued its use of the drug, but explained its action on the ground that it dilated the peripheral blood-vessels. In the light of recent scientific investigation, however, this theory of its mode of action can be no longer retained, and the fact that the drug is rapidly falling out of popularity in these conditions would indicate that clinically it has not shown the virtues which the eclectics attributed to it.

Veratrum has, however, an important field of usefulness. In cases of too high blood-pressure in which nature has not already slowed the pulse, the great reduction in the frequency of the heart beat will often reduce the hypertension with less disturbance of the integrity of the circulation than any measure of equal power. It is probably to its power of lowering blood-pressure that its beneficent effects in puerperal eclampsia are to be attributed, rather than to its depressant action upon the spinal cord.

In cases of tachycardia of various origins, such as the so-called irritable heart of athletes or the rapid pulse of Graves's disease, it is one of our most reliable stimulants of inhibition.

Veratrum is also a very valuable drug in the treatment of certain types of valvular lesion of the heart. Its favorable influence in these conditions is due solely to the reduction in the rapidity of the heart action which, as explained on page 179, encourages the upbuilding of the reserve power of the heart. The slowing of the pulse is produced solely through stimulation of the inhibitory mechanism, and as this governs not only the rapidity of the heart but also the tonus of the muscle, veratrum tends to increase the relaxation of the heart, and, theoretically at least, might under some circumstances contribute to the production of dilatation. On the other hand, if the ventricular tone be not already greatly reduced in cases of mitral lesions the completeness as well as the duration of the diastole may directly assist the heart in the economical performance of its function.

Although veratrum viride is a remedy of great power, capable of producing the most alarming symptoms, yet it is the safest of the cardiac sedatives. Overdoses of it provoke vomiting so soon and so certainly that it is somewhat doubtful whether a robust adult could be killed by a single dose of any of its official preparations, especially if prompt and judicious treatment were afforded.

Toxicology.—The symptoms of the poisoning by this drug are violent and repeated vomiting with great muscular weakness and extreme slowing of the pulse and of the respiration. If death should occur, it is due to the respiratory failure. In the treatment vomiting should be encouraged by large draughts of warm water until the stomach is well washed out. Then the patient should be forced to lie flat upon the back, with the head lower than the feet, and the efforts at vomiting should be restrained. If they cannot be checked, and if the prostration be severe, on no account should the patient be allowed to rise up, but must be made to vomit into a towel. A full dose of laudanum should be given by the rectum, and brandy or whiskey be administered by the mouth. If the pulse is slow, atropine should be employed, as it antagonizes the action of the poison not only on the cardio-inhibitory mechanism but also on the respiration. Camphor and strychnine should be given hypodermically.

VERATRINE.

This alkaloid, which is more properly known as cevadine, is obtained from the seeds of the *Asagræa officinalis,* or sabadilla,* a Mexican liliaceous plant. Traces of the alkaloid appear to exist also in *Veratrum viride,* although not in *Veratrum album.* As found in commerce, it is almost always more or less impure, and occurs as a grayish-white powder of an intensely acrid taste, and producing, even in the minutest quantity, when smelled frequently repeated sneezing, which may continue for hours. An ointment containing 4 per cent. is official. The alkaloid is occasionally used internally in doses of 1/30 grain (2 milligm.).

Physiological Action.—Locally veratrine is intensely irritant to either skin or mucous membrane, and appears to have some local anæsthetic effect also. Its most interesting action is its effect upon muscle. It affects the striated muscle-tissue in such a way that the contraction following a single electrical shock, instead of relaxing immediately as in the normal condition, may require several seconds for complete relaxation.

According to Pilcher and Sollmann, cevadine causes slowing of the pulse through stimulation of the cardio-inhibitory center and thereby lowers the blood-pressure.

The only therapeutic use for which there is any justification is as counterirritant in neuralgia and allied conditions. It is actively toxic, however, and presents no advantage over other counterirritant remedies.

* The action of *sabadilline,* the congeneric alkaloid of veratrine, has been partially studied by I. Urpav (*Montpellier Méd.,* 1883, i, 274), who finds it to have only about one-twelfth the toxic power of veratrine.

ACONITE.

Materia Medica.—The *Aconitum napellus,** or monkshood, is a tall perennial, indigenous in Europe, and cultivated in this country for the sake of its spike of blue flowers. The leaves are three or four inches in diameter, and cut almost to the base into from three to seven three-lobed, wedge-shaped divisions.

The root, which is the only official portion, is from three to four inches long, very tapering, about three-quarters of an inch in diameter at the base. Its taste is bitterish, acrid, and after a little while benumbing, giving origin to intense tingling of the lips and mouth. It may be distinguished from *horseradish root,* with which it has been sometimes fatally confounded, by its external brown color and its lack of odor when scraped. The whole plant is active and tastes like the root. The United States Pharmacopœia requires that the root shall contain not less than 0.5 per cent. of alkaloids.

In 1833 Geiger and Hesse discovered in aconite the alkaloid *aconitine.* According to the most recent researches, there are in the root, however, besides aconitine, two alkaloids, *benzaconine* and *aconine,* which may also be made by the hydrolysis of aconitine, benzaconine being the *isaconitine,* and the principal constituent of the *napelline* and the *picraconitine* of older writers (Cash and Dunstan).

Aconitine occurs in colorless or whitish, odorless, rhombic tables or prisms. In extremely dilute solution it is capable of producing a characteristic tingling of the tongue or lips, but is so poisonous that it should never be tasted unless in solution of greater strength than one part in five thousand, and even then with great caution. *Amorphous aconitine* of commerce is a more or less impure mixture, containing decomposition products.

Official Preparations:

Fluidextractum Aconiti	1 to 2 minims (0.06–0.12 mil).
Tinctura Aconiti (10 per cent.)	5 to 15 minims (0.3–1.0 mil).
Aconitina	$\frac{1}{400}$ grain (0.16 milligm.).

Physiological Action.—Aconite and aconitine are locally irritant, but this irritant influence is soon overwhelmed by the effect of the drug upon the peripheral ends of the sensory nerves, so that numbness and tingling are produced at the point of application. Moreover, the general influence of the drug is so overwhelming that the local effect counts for very little in practical medicine.

Absorption and Elimination.—Aconite yields its alkaloids with great rapidity to absorption, and aconitine is capable of passing through

* All species of the genus Aconitum are more or less poisonous, although *A. napellus* is the only one official. For a study of the comparative strength of the various aconites, see Schroff (*Journal für Pharmacodynamik,* 1857, 335).

Pseudaconitine, the alkaloid of *Aconitum ferox,* has been physiologically studied by Boehm and Ewens (*A. E. P. P.,* 1873, i) and by Cash and Dunstan (*P. Tr. R. S. L.,* Series B, 1902), who are in accord in finding that its physiological action is that of aconitine save only in regard to strength.

the mucous membranes and even the skin, making it, in pure form, a dangerous external remedy. Concerning its elimination we have no knowledge.

Circulation.—The effects of aconite on the circulation are complex and the changes produced by toxic doses not clearly understood. It produces first a slowing of the pulse with a fall in the blood-pressure. The slowing of the pulse is due chiefly to stimulation of the cardio-inhibitory centers, although there is some evidence that the drug affects also the peripheral endings of the pneumogastric nerve. The fall of blood-pressure is caused chiefly by the slowing of the pulse, since section of the vagi is followed by an immediate increase both in the rate of cardiac pulsations and in the arterial pressure. It is probable, however, that even with non-toxic doses there is more or less weakening of the heart muscle. After large doses there is lowering of the blood-pressure, even with the vagi divided, which is to be attributed to a depressant action directly upon the heart muscle. The vasomotor system does not seem to be affected by therapeutic doses.

After a poisonous dose there may be seen most extraordinary irregularities of the heart action. According to Hartung the first toxic manifestation of aconite upon the heart is an increase in the irritability of the ventricular muscle with the production of extra systoles, the ventricular rate and consequently the pulse-rate being very rapid, while the auricular beats are not abnormally frequent. Later in the poisoning there is a reduction in the irritability of the ventricular muscle and the refractory phase of the ventricle becomes prolonged so that it does not respond to every contraction of the auricle; in other words, the ventricular rate is slower than the auricular. The lack of coördination between the changes of the heart must seriously interfere with the coronary supply, which will add to the weakness of the muscle produced directly by the drug. The heart finally stops beating in a position of complete relaxation, the muscle being non-responsive to either electrical or mechanical irritation.

Motor System.—Aconite exercises comparatively little influence on the voluntary muscles, but very large doses do produce more or less alteration in the form of the muscle curve.

Upon the central nervous system in the mammal the drug has very little effect. In the frog, however, there is a loss of reflex activity, with at first a preservation of voluntary motion, showing that the absence of reflexes is due to a paralysis of some portion of the sensory system. This early paralysis of the sensation appears to be chiefly due to an effect upon the peripheral endings of the afferent nerve-fibers. Mackenzie found that when a nerve is protected from the poison by tying its supplying artery irritation of this nerve gave rise to reflex response when the remainder of the frog's periphery was insensible. Later there occurs also the paralysis of the sensory ganglia of the cord, and probably, finally, a depression of the motor side of the cord as well.

Therapeutics.—Aconite is used clinically for the purpose of quieting the heart in conditions of overaction, especially in cases of chronic heart disease. Where only a moderate effect is required, aconite is generally preferable to veratrum, because less prone to disturb the stomach. On the other hand, where the remedy is being pushed to the full limit, veratrum is not only a more powerful but also a safer drug, as the overdose is likely to provoke emesis. Aconite is frequently used in the treatment of mild febrile complaints. Its virtue in these conditions depends upon its influence on circulation. The slowing of the heart tends to preserve the functional power of the organ, but more important is the lowering of the blood-pressure, which aids in the secretion of sweat and thereby tends to lower bodily temperature.

Because of its locally anæsthetic action, aconite is used as a topical remedy in the treatment of neuralgias, and other peripheral pains. It has been even employed for its local action upon the sensory nerves of the stomach to allay vomiting. Since, however, it is capable of being absorbed by the skin as well as other mucous membrane, the external application of aconite is not free from danger, and its use as a local anæsthetic should not be encouraged.

Toxicology.—After ingestion of a toxic dose of aconite, the first and most characteristic symptom in most cases is a burning or tingling in the throat or in the extremities, soon spreading over the whole body. The pulse rapidly falls in frequency, and in a very little time becomes exceedingly weak, intermittent, irregular, and finally imperceptible; the muscular strength is greatly reduced and sometimes almost entirely gone; the respirations are shallow, feeble, irregular, and infrequent; the general sensibility is very much benumbed, and marked anæsthesia of the surface may be present; the skin is bedewed with cold sweat; the countenance is anxious, sunken, livid, and the eyes are often protruded, or are even spoken of as glaring; the pupil is generally dilated, but, when there are no convulsions, may be contracted; gastric burning is sometimes complained of, and severe vomiting may be present, but the stomach is not rarely retentive. The intellect generally remains unaffected until very near the close, sometimes to the very moment of death. In the collapse of the latter stages of aconite poisoning the special senses may be lost, especially the sight. The voice is very generally extinguished. Convulsions occur in some cases, not in others; and certainly in some instances, if not always, the patient is unconscious during their continuance. Diplopia, or other disorder of vision, has been noted in some cases. Death may occur suddenly, especially *directly after some exertion* on the part of the patient, from syncope.

The symptoms usually come on in a very few minutes. In the shortest case we have met with, death occurred in thirty minutes. The average time (Reichert) is three and a third hours, the longest recorded case being five and a half hours. Five grains of an extract and eighty minims of a tincture are said to have caused death.

The only diagnostic symptom of aconite poison is the peculiar tingling which is probably always present, although in suicidal cases the patient may refuse to reveal it, or in advanced poisoning unconsciousness may prevent its being told. In a case of poisoning with marked prostration and circulatory weakness and collapse, in the absence of the vomiting, purging, or disorder of the pupil, or any similar diagnostic symptom, a presumptive diagnosis may be made of aconite poisoning.

The first indication for treatment in aconite poisoning is evacuation of the stomach; as emetics usually fail, on account of the local gastric anæsthesia, the stomach-pump may be used, but the danger of causing fatal collapse in extreme cases must not be overlooked. Tannic acid may be administered as an imperfect antidote. Hot concentrated alcoholic stimulants should be freely given; strychnine, atropine, and digitalis should be used hypodermically with great boldness, tempered with caution. Ammonia may be injected into the veins, if it be found practicable. The patient must be kept upon the back, with the feet a little higher than the head, and external heat be used freely to maintain temperature. Laborde and Duquesnel affirm that in the lower animals death after a usually fatal dose of aconitine can be prevented by artificial respiration; and in a case of human poisoning, if the heart's action were at all sustained, and the respiration failing, artificial respiration might be resorted to.

NITRITES.

Materia Medica.—The nitrite ion is liberated in the system not only by the salts of nitrous acid but also by certain nitric acid esters. Of the compounds of nitrous acid there are recognized by the Pharmacopœia amyl nitrite, ethyl nitrite, and sodium nitrite, and of the esters of nitric acid the only one at present recognized by the United State Pharmacopœia is the trinitrate of glycerol, commonly known as nitroglycerin, although the erythrol tetranitrate is used to a considerable extent.

Amyl nitrite is a yellowish, oily liquid, extremely volatile, with a characteristic fruity odor, which is made by the action of nitric acid upon amyl alcohol. It is a mixture of various esters containing about 80 per cent. of amyl (chiefly iso-amyl) nitrite.

Sodium nitrite (this should be carefully distinguished from sodium nitrate) occurs in the market usually in white pencils; it has a mild saline taste and when exposed to the air deliquesces and is gradually oxidized into the nitrate. It is freely soluble in water.

Ethyl nitrite is official in the form of a four per cent. solution (*spiritus ætheris nitrosi*). This is a volatile inflammable liquid of a pale yellow color with a fragrant ethereal odor.

Glyceryl trinitrate, or nitroglycerin, although it is a salt of nitric acid, affects the system similarly to the salts of nitrous acid, probably

being reduced in the body. It is official in the form of a one per cent. solution. Tablets of nitroglycerin, although not official, are largely employed. They are very likely, however, to contain much less of the nitroglycerin than stated in the label, as this principle, being volatile, is largely evaporated unless they are carefully protected.

The nitrites are *incompatible* with antipyrine, the iodides, the bromides, and ferric sulphate.

Official Preparations:

Amylis Nitris .....1 to 5 minims (0.06–0.30 mil).
Sodii Nitris .....1 to 3 grains (0.06–0.20 Gm.).
Spiritus Ætheris Nitrosi (4 per cent. Ethyl Nitrite) .....30 to 90 minims (2–6 mils).
Spiritus Glycerylis Nitratis (1 per cent. Nitroglycerin) (Spiritus Glonoini).....1 to 3 minims (0.06–0.18 mil).

Physiological Action.—*Circulation.*—Although the pulse is generally much increased in frequency by the nitrites, the arterial pressure is greatly diminished, and by sufficient doses reduced almost to zero. As the number of heart-beats is increased rather than diminished, and the output of the individual beat not perceptibly lessened, it is evident that, at least in the early stages of the nitrite action, the lowering of arterial tension must be due to dilatation of the blood-vessels. This conclusion has been confirmed directly by various experimenters who have shown, first, an increase in the caliber of the blood-vessels, especially in the splanchnic area, by plethysmographic methods, and also a more rapid flow of blood through the arterial system. In small doses there seems to be an especial degree of action on the skin vessels, as shown by the flushing of the face which is caused by the nitrites. The action on the pulmonary arterioles seems to be different from that on the general circulation, as authorities are unanimous that there is an increase in the blood-pressure in the pulmonary artery. The action of the nitrites upon the blood-vessels is chiefly a peripheral one, as is shown by the facts that when perfused through isolated organs under constant pressure it increases the rate of flow and that it antagonizes epinephrine.

Concerning the action of the drug upon the heart muscle the evidence is not conclusive; although certain observers have claimed to have found some increase in the working power of the isolated frog's heart after small doses of the nitrite, others have failed to obtain any sign of stimulation. The increase in the size of the pulse-wave frequently seen after the injection of nitrites is attributable rather to the lessening of the resistance through vascular relaxation than to any stimulant influence on the heart muscle. In the intact animal the output of the heart will be increased both through the shortening of the diastolic period and the diminished resistance before the heart. Since the pneumogastric nerve retains its irritability even after large

doses of the nitrite, and since this group of remedies is incapable of accelerating the pulse after previous section of this nerve, it is evident that the increase in the pulse-rate is owing to the paralysis of the cardio-inhibitory centers in the medulla.

Large doses of the nitrites cause the blood to take on a brownish hue. This is due to the formation of a new compound with the hæmoglobin; whether this new compound is identical with methæmoglobin is at present doubtful. This derivative of hæmoglobin, while not absolutely incapable of yielding up this oxygen to the tissues, is a much more stable compound than oxyhæmoglobin, so that in cases of nitrite poisoning there is an oxygen hunger and consequently a marked increase in the respiratory rate, although the nitrites cannot be classed

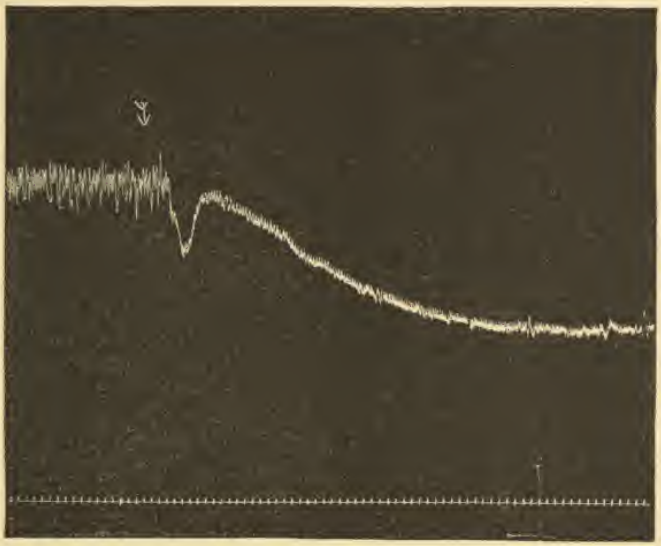

FIG. 23.—Showing effect of sodium nitrite on the circulation. It lowers the pressure by dilating the vessels and increases the pulse-rate by paralyzing the cardio-inhibitory centers. Time marker indicates 5 seconds.

in any proper sense as respiratory stimulants. Haldane, Makgill, and Mavrogordate have found that animals in an atmosphere of pure oxygen will survive doses which are certainly fatal under ordinary conditions.

Nervous System.—As was first shown by H. C. Wood, the nitrites cause a diminution in the reflex activity, due to a depressant action upon the spinal cord, since even after fatal doses the nerves and the muscles retain their functional power. This action seems to be limited purely to the motor tracts of the spinal cord when the drug is given in therapeutic doses, although after very large quantities there is some evidence of a lessened irritability of the peripheral motor nerves.

Therapeutics.—*Circulation.*—The nitrites are our most certain agents for the reduction of high arterial tension. Indeed, in many conditions they are the only drugs available. They were introduced into medicine by Sir Lauder Brunton in 1867, who, believing from the sphygmographic tracings that angina pectoris was due to arterial spasm, suggested the use of amyl nitrite as a powerful and rapidly acting vasodilator. Whatever view one may take of the pathology of this condition, there is no room for doubt that in many cases this remedy will afford almost instantaneous relief of the paroxysms of pain characteristic of angina pectoris.

The nitrites are also widely employed for their reduction of too high arterial tension in the pre-sclerotic stages of arterial fibrosis. When actual degeneration has taken place in the arteries, although they are widely used, but little benefit can be hoped from their employment; their action is essentially upon the muscles of the walls of the arteries, and it is manifest that where muscle-tissue is replaced with lime salts, or even with fibrous tissue, the nitrites cannot effect a dilatation of the vessels. Certain cases of migraine appear to be dependent on paroxysms of vascular spasm, and in these cases the nitrites are often capable of aborting the attack. They have also been used to guard against the vasomotor action of digitalis in certain cases of chronic heart-disease, but in many cases not with good judgment. The nitrites have been recommended in the treatment of the early stages of pneumonia with the idea that by their dilating effect upon the general blood-vessels and their constricting effect upon the pulmonary blood-vessels they would lessen the area of congestion in the lungs. The danger of this disease, however, lies not in the amount of lung tissue involved but in the degree of toxæmia, and it is doubtful whether in true pneumonia the nitrites are of any service. It is probable their effect in lessening the amount of blood passing through the lungs explains their value in pulmonary hemorrhage, on which point there is much clinical evidence.

Small doses of the nitrite, as mentioned previously, seem to dilate especially the vessels of the skin; they are, therefore, useful whenever it is desired to determine the flow of blood to the surface. Thus they are of much service to aid in the production of diaphoresis, either in combination with other sudorifics or in connection with a hot bath. It is this effect which has made the sweet spirits of nitre so popular a remedy in the treatment of febrile complaints. So powerful is their influence upon the peripheral vasomotor mechanism that they are capable of aborting the algid stage of the malaria paroxysm, although they have no influence on the course of the disease.

The nitrites, especially nitroglycerin, have been largely used as circulatory stimulants in various forms of so-called heart-failure, especially when very acute, such as the collapse following injuries or occurring during the course of anæsthesia. There is no reason, either clinical or experimental, to believe that they can be of any benefit in

this class of conditions, and if freely used they certainly are capable of doing much damage. While by depressing the inhibitory centers they increase, in the normal animal, the output of the heart, their vasomotor effects always outweigh any possible stimulation of the heart, and the tendency of the blood-pressure is always downwards; this is true whether the arterial tension be high, low, or normal.

The Nervous System.—The nitrites are of much value for the control of certain convulsive disorders. Thus in strychnine poisoning the promptness and power of amyl nitrite make it one of the most valuable remedies we possess; during the paroxysms of cramp asphyxia of the strychnine convulsion, when the rapidly acting depressants, which are ordinarily administered by inhalation, cannot be administered, amyl nitrite may be injected hypodermically. In tetanus the nitrites are of little value because of the fugaciousness of their effects, nor can they be repeated with indefinite frequency because the patient soon forms a tolerance for them. These drugs are also of service for the relief of puerperal convulsions, but if employed immediately after labor there is danger of producing serious postpartum hemorrhage through uterine relaxation.

The nitrites in full dose are certainly capable of interrupting the epileptic paroxysm, but in ordinary circumstances there is no great advantage to be gained from this effect. In that condition, however, known as status epilepticus, in which the patient passes from one convulsion into another, they are useful for ending the series of spasms. Also in those rare cases of epilepsy when the fit is preceded by an aura, the inhalation of amyl nitrite immediately on the appearance of prodromal symptoms will generally abort the attack.

Amylnitrite is often of service during the paroxysm of asthma. Its beneficial effects are probably due largely to a relief of the congestion of the mucous membrane, brought about by the dilatation of the blood-vessels in the splanchnic area, but the experiments of Baehr and Pick indicate that they are also due in part to the narcotic effects of the amyl radical.

Administration.—The physiological action of all nitrites is precisely the same. The choice between them is governed chiefly by the rapidity with which they produce their effects. The most speedy is the amyl nitrite, the effects of which begin generally within thirty seconds and last from five to ten minutes. The action of nitroglycerin, when taken by the mouth, usually begins to manifest itself within one or two minutes, and rarely lasts, after ordinary doses, more than half an hour. Sodium nitrite is distinctly slower in its effects, and its influence may be manifest for as long as two hours after its ingestion. Slower than any of the official preparations, however, is the erythrol tetranitrate. In cases where immediate action is desired, as in angina pectoris or the epileptic aura, amyl nitrite will be the preparation of preference. This is generally dispensed in thin glass capsules, known as "pearls," containing from three to five minims. One of these

is broken in the handkerchief and rapidly inhaled. Where a continuous effect is desired neither amyl nitrite nor nitroglycerin is of any value: the administration of nitroglycerin three times a day, as is not infrequently done in cases of chronic circulatory disorders, is silly. Sodium nitrite is much more suitable for these cases, but unfortunately often produces very unpleasant gastric disturbances. According to the observations of Laurence none of the nitrites can keep the blood-pressure low for more than a few days.

Nitroglycerin may be administered either by the mouth, in the form either of the official spirits or of tablet triturates, or hypodermically. It must be remembered that it is a volatile substance and the tablet triturates lose their potency if kept for a length of time; they should, therefore, preferably be freshly made.

Sodium nitrite, because of its deliquescence, cannot be administered in any form save in solution. Erythrol tetranitrate is usually employed in the form of tablets.

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CHAPTER V.

DRUGS USED TO AFFECT THE ALIMENTARY TRACT.

STOMACHICS.

Stomachics are drugs which by virtue of their effect upon the mucous membrane of the stomach tend to increase gastric digestion. They are divided into the *bitters* and *aromatics*. The term "simple bitter" is applied to bitter substances of vegetable origin which have no influence upon the system but are used solely to affect the functional activity of the stomach. Borrissow found that the introduction of tincture of gentian into the mouth of the dog in conjunction with the presentation of food produced a greater flow of gastric secretion than did the food alone, and believed that this action was a reflex one, depending upon the bitter taste. More recent investigators, however, have called in question this observation, and Carlson, in an elaborate study upon dogs and man, was unable to find any evidence of increased secretion or movements in the stomach from the administration of any of the commonly used simple bitters. Moorhead, however, working in Carlson's laboratory, found that, while the bitters did not affect gastric activity in normal animals, in dogs rendered anæmic by repeated bleedings they increased both the quantity and the acidity of the gastric juice. This action was partly due to a reflex effect through the gustatory nerve and partly to the direct action on the gastric mucosa. While the scientific evidence as yet is not strong enough to establish definitely the mode of action of the bitters, it tends to confirm rather than contradict the almost universal conviction of clinicians that in many conditions of depraved digestion and appetite these drugs exercise a valuable influence.

QUASSIA.

Under the name quassia the United States Pharmacopœia recognizes the wood of the *Picrasma excelsa* (Jamaica quassia), a large tree growing in the island of Jamaica, and of the *Quassia amara* (Surinam quassia), a shrub found in Guiana and neighboring parts of South America. Each of these contains a bitter principle; these, while closely allied chemically, are not regarded as identical. The precise chemical nature of these principles, which are known respectively as picrasmin and quassin, is not clearly understood.

The only official preparation is the tincture (*Tinctura Quassiæ*), the dose of which is one-half to one fluidrachm (2–4 mils).

Physiological Action.—Although in large doses quassin produces symptoms of systemic poisoning in frogs, its only effects in man are those which are due to its local action. It is sufficiently irritant that in overdose it is capable of producing nausea, vomiting, and diarrhœa; also evidence of irritation of the kidney.

Therapeutics.—Quassia is probably the most actively stimulating

of the simple bitters, and may be used wherever such remedies are indicated. It is also widely employed for the destruction of seat-worms in the form of an infusion, two ounces to one pint; it affords a most harmless and efficient injection. Its exhibition should be preceded by an enema of simple water, so as thoroughly to wash out the rectum and allow access to every fold of the rectal mucous membrane.

GENTIAN.

The root of *Gentiana lutea,* the yellow gentian of the Alps. This root occurs in the shops either in pieces of various sizes and shapes, but usually several inches in length, or else in transverse slices. The texture is spongy, the odor faint but peculiar, and the taste bitter. It contains *gentisic acid,* which was discovered by Leconte and is tasteless and physiologically inert. The active principle is probably the *genito-pikrin* of Kromayer, a neutral, crystalline substance, of an intensely bitter taste.

Official Preparations:

Extractum Gentianæ .....2 to 4 grains (0.13–0.26 Gm.).
Fluidextractum Gentianæ .....10 to 30 minims (0.06–2.0 mils).
Tinctura Gentianæ Composita (10 per cent.)..1 to 4 fluidrachms (4–16 mils).

Therapeutics.—Gentian is one of the most efficient of the simple bitters, and may be used whenever such a remedy is indicated. The most largely used of its preparations is the compound tincture, which contains gentian, bitter orange peel, and cardamom.

CALUMBA.

The root of *Jateorhiza palmata,* a climbing vine of Mozambique. It occurs in the shops in transverse disk-like slices, oval or circular in outline, one or two inches in diameter, of a spongy texture, having a yellowish surface, a very bitter taste, and a slightly aromatic odor. It contains a great deal of starch, besides berberine, and, in lesser amount, *columbin,* a bitter neutral principle crystallizing in rhomboid prisms or needles.

The dose of the tincture is 1 to 2 fluidrachms (4–8 mils).

AROMATICS.

Volatile Oils.—The group of stomachics spoken of as the aromatics depend for their activity upon the presence either of a volatile oil or an oleoresin—that is, a combination of volatile oil and resin. The so-called ethereal, or volatile, oils contain bodies of the most varying chemical composition; thus we have the terpenes—combinations of carbon and hydrogen—alcohols, phenols, sulphur compounds, etc. As would be expected in such a chemically diverse group, the volatile oils differ widely in their physiological and medicinal properties. All of them, however, are more or less locally irritant and consequently may

excite the alimentary tract to greater secretion or more active peristalsis. Many of them are capable of being absorbed and may exercise a local irritant action upon the kidneys, and hence be useful as diuretics; among these may be mentioned especially the oils of turpentine and juniper. In a similar manner they may stimulate the bronchial mucous membrane and be useful in chronic bronchitis; in this regard the oils of turpentine, of anise, of cloves, and of cinnamon may be mentioned. It is probable that the diaphoretic effects of various teas made from aromatic plants, which form so popular medicaments in household therapeutics, are due in part to the volatile oils they contain, as well as to the heat and water.

Many of the volatile oils are powerful germicides. To this class belong especially those oils which contain phenol derivatives, as cinnaldehyde from oil of cinnamon, eugenol found in oil of cloves and oil of bay, saffrol found in oil of sassafras and oil of camphor, and thymol from the oil of thyme. While our knowledge of the germicidal power of the volatile oils is regrettably incomplete, it is evident that many of them are extremely active; thus Calvello states that oil of cinnamon is one-seventh as active as corrosive sublimate, and Martindale assigns the following phenol coefficients: oil of thyme, 15; oil of cloves, 9; of cinnamon, 8; of cassia, 5, and of wintergreen, 5. Peck found that the oil of cassia was antiseptic when present in 1 to 2200, the oil of cloves 1 to 1100, the oil of sassafras 1 to 1000, and the oil of peppermint 1 to 800.

While many of the volatile oils possess marked local anæsthetic properties, the only ones which are used extensively for this action are the oils of peppermint and cloves.

The action of the aromatics upon the digestive organs differs from the bitters, in that they are more powerful and more transient and appear to affect intestinal as well as gastric digestion. They are used:

(1) To excite the digestive secretions. For this purpose they are generally used in conjunction with bitter tonics, but also are frequently employed in the form of condiments by themselves.

(2) To excite intestinal peristalsis, most frequently to expel flatus. Under this head may also come their use in cathartic mixtures to prevent griping.

(3) As vehicles. This is probably the most important and most frequent use of the majority of the aromatics. They are especially useful for this purpose to disguise the taste of bitter substances, although they are useful also to a lesser extent to cover many other unpleasant flavors.

(4) Some of them are used as local applications, either for their antiseptic or anæsthetic powers.

The volatile oils are contra-indicated in the inflammatory states of the stomach or bowels. In passive congestions, as in alcoholic gastritis or chronic serous diarrhœa, they are, however, often agents of great value.

Official Preparations:

The following are the official preparations whose activity is chiefly owing to a volatile oil:

Oleum Amygdalæ Amaræ .....¼ to ½ minim (0.02–0.03 mil).
Benzaldehyde .....¼ to ½ minim (0.02–0.03 mil).
Spiritus Amygdalæ Amaræ (1 per cent.)....10 to 20 minims (0.6–1.3 mils).
Aqua Amygdalæ Amaræ .....Vehicle.

Oleum Anisi .....3 to 5 minims (0.2–0.3 mil).
Aqua Anisi .....Vehicle.
Spiritus Anisi (10 per cent.).....½ to 1 fluidrachm (2–4 mils).

Oleum Aurantii .....3 to 5 minims (0.2–0.3 mil).
Spiritus Aurantii Compositus (Oils of Orange, Lemon, Coriander and Anise).....15 to 30 minims (1–2 mils).
Syrupus Aurantii .....Vehicle.
Tinctura Aurantii Dulcis.....Vehicle.
Elixir Aromaticum (1.2 per cent. of Compound Spirit of Orange).....Vehicle.
Elixir Glycyrrhizæ (Aromatic Elixir and Fluidextract of Licorice).....Vehicle.
Fluidextractum Aurantii Amari.....15 to 30 minims (1–2 mils).

Tinctura Cardamomi .....1 to 2 fluidrachms (4–8 mils).
Tinctura Cardamomi Composita.....Vehicle.

Oleum Caryophylli .....3 to 5 minims (0.2–0.3 mil).
Eugenol—Synthetic Oil of Cloves.....3 to 5 minims (0.2–0.3 mil).

Oleum Cassiæ (Oil of Cinnamon) .....1 to 3 minims (0.06–0.2 mil).
Spiritus Cinnamomi (10 per cent.).....15 to 30 minims (1–2 mils).
Aqua Cinnamomi .....Vehicle.
Tinctura Cinnamomi .....1 to 2 fluidrachms (4–8 mils).

Oleum Fœniculi .....3 to 5 minims (0.2–0.3 mil).
Aqua Fœniculi .....Vehicle.

Oleum Lavandulæ .....3 to 5 minims (0.2–0.3 mil).
Spiritus Lavandulæ (5 per cent.).....½ to 1 fluidrachm (2–4 mils).
Tinctura Lavandulæ Composita.....½ to 1 fluidrachm (2–4 mils).

Oleum Limonis .....3 to 5 minims (0.2–0.3 mil).
Tinctura Limonis Corticis.....Vehicle.

Oleum Menthæ Piperitæ.....3 to 10 minims (0.2–0.6 mil).
Menthol .....1 to 2 grains (0.06–0.12 Gm.).
Spiritus Menthæ Piperitæ (10 per cent.)....½ to 1 fluidrachm (2–4 mils).
Aqua Menthæ Piperitæ.....Vehicle.

Oleum Menthæ Viridis.....3 to 5 minims (0.2–0.3 mil).
Spiritus Menthæ Viridis (10 per cent.).....½ to 1 fluidrachm (2–4 mils).
Aqua Menthæ Viridis.....Vehicle.
Oleum Cari (Caraway).....3 to 5 minims (0.2–0.3 mil).
Oleum Coriandri .....3 to 5 minims (0.2–0.3 mil).
Oleum Myristicæ .. ..3 to 5 minims (0.2–0.3 mil).
Oleum Pimentæ .....3 to 5 minims (0.2–0.3 mil).

Oleum Rosmarini .....3 to 5 minims (0.2–0.3 mil).
Oleum Sassafras .....3 to 5 minims (0.2–0.3 mil).
Pulvis Aromaticus (Contains Cinnamon, Ginger, Cardamom and Nutmeg).....5 to 15 grains (0.3–1.0 Gm.).
Fluidextractum Aromaticum (100 per cent. of Aromatic Powder) .....5 to 15 minims (0.3–1.0 Gm.).

The OIL OF BITTER ALMONDS (*Oleum Amygdalæ Amaræ*) contains from 2 to 4 per cent. of hydrocyanic acid and hence is actively poisonous. The bitter-almond flavor may be given to mixtures more safely by the use of benzaldehyde.

OIL OF WINTERGREEN (*Oleum gaultheriæ*) is no longer official. The wintergreen flavor, however, may be obtained by the use of methyl salicylate (see page 376).

OIL OF PEPPERMINT is one of the most widely popular flavors of this class, and its water is probably used more extensively than any other aqueous vehicle. Oil of peppermint contains 50 per cent. of a secondary alcohol known as menthol or as peppermint camphor.

MENTHOL occurs as colorless crystals with a strong characteristic odor, producing a sensation of coolness when tasted or smelled or when applied to the skin. It is almost insoluble in water but freely soluble in alcohol and the fixed oils. The sensation of coldness which follows its local application is due apparently to a stimulant effect upon the so-called nerves of coldness. It is also locally anæsthetic.

It is mildly irritant and an active antibacterial agent, probably surpassing phenol in germicidal powers. According to Weinsche it is antiseptic in proportion of one in three thousand.

Menthol is a remedy of great value in the treatment of various irritative conditions of mucous membranes and skin, such as pruritus ani, urticaria and the like. Partly because of its local anæsthetic action and partly because of its antiseptic powers, it is also widely employed as a topical application in acute inflammations of the nose and throat. For this purpose it is generally used in the form of a one per cent. solution in liquid petrolatum. S. A. Russell asserts that a ten to fifty per cent. solution of menthol will often abort boils, carbuncles, and other superficial abscesses. The application of a strong menthol solution or rubbing with the menthol pencil will often relieve neuralgic pains of superficial origin. The action of oil of peppermint is practically that of its menthol. It is widely used as a carminative and as a local anæsthetic and antiseptic in conditions of nausea.

CLOVES are the unexpanded flowers of *Eugenia aromatica,* a tree native to the Molucca Islands. This source, however, is practically exhausted, and the present supply comes from cultivated trees in the West Indies, the islands of the Indian Ocean, and other tropical regions. They owe their properties to an exceedingly pungent volatile oil, yellowish when fresh, but becoming darker with age. The oil of cloves should contain not less than eighty per cent. of *eugenol.* This latter is an unsaturated phenol corresponding in its physical properties to the oil of cloves. Oil of cloves, besides being used as a carminative and an aromatic, is often employed to benumb sensitive dentine, or

even exposed pulp, in caries of the teeth. Dropped on a piece of cotton and placed in the cavity, it is much used to relieve toothache.

Clove tea, two drachms to the pint, an infusion made with boiling water, is often used domestically in doses of a wineglassful or more for acute menstrual suppression and as a sudorific.

Nutmeg (*Myristica*) is the kernel of the ripe seed of *Myristica fragrans,* a tree growing in the Molucca Islands. The nutmeg contains both a fixed and a volatile oil. *Mace* (U. S. P., 1890) is the arillus or outer imperfect supernumerary coating of the seed. The aromatic flavor of both mace and nutmeg is due to the presence of a volatile oil which is recognized by the United States Pharmacopœia. This oil contains a solid ester known as myristicin which is a narcotic poison of considerable power. It causes in the lower animals ataxia and tremors followed by coma and paralysis, death being due to failure of respiration. After fatal doses there has been found fatty degeneration of the liver. Although to produce narcosis in the lower animals requires quantities which are likely to prove fatal, in man one or two nutmegs will usually suffice to produce a dreamy, half-conscious intoxication. A few cases of fatal poisoning in the human being have been reported. The symptoms have been dizziness, stupor deepening into coma, muscular relaxation, dilated pupils, slow pulse and respiration, and suppression of urine, ending in death from respiratory paralysis.

A second group of aromatics depend for their activity upon the presence of oleoresins. This group of remedies are much more powerful irritants than those which contain simply volatile oil.

Official Preparations:

Capsicum ..... 1 to 3 grains (0.06–0.2 Gm.).
Oleoresina Capsici * ..... ¼ to ½ minim (0.01–0.03 mil).
Tinctura Capsici (10 per cent.) ..... 5 to 15 minims (0.3–1.0 mil).

Piper ..... 5 to 10 grains (0.3–0.6 Gm.).
Oleoresina Piperis ..... ½ to 1 gram (0.03–0.06 Gm.).
Piperina ..... 3 to 5 grains (0.2–0.3 Gm.).

Oleoresina Zingiberis ..... ½ to 2 minims (0.03–0.12 mil).
Fluidextractum Zingiberis ..... 5 to 10 minims (0.3–0.6 mil).
Tinctura Zingiberis (20 per cent.) [Essence of Ginger] ..... ½ to 1 fluidrachm (2–4 mils).
Syrupus Zingiberis (3 per cent.) ..... Vehicle.

Ginger (Zingiber) is the dried rhizome or root stock of *Zingiber officinale,* growing in the East and West Indies. It loses its activity upon exposure, and the fresher the ginger the greater its power. Ginger is much used as a stimulant carminative in colic, as an addition, in the form of its oleoresin, to cathartic pills, and also in the

* The name of *Capsicin* has been applied by different observers to the oil, to the resin, and to their combination, but has no definite meaning.

treatment of alcoholic gastritis. A hot infusion is much used in domestic medicine under the name of ginger tea for the relief of intestinal colic or suppression of the menses, especially when due to exposure to cold.

Pepper (piper) is the unripe fruit of the *Piper nigrum*, a woody vine of the East Indies. It contains, besides its volatile oil, an acrid resin and a feebly basic crystalline body, known as piperine. The latter, when pure, is tasteless, but very commonly has a burning taste, due to contamination with volatile oil. Piperine was at one time believed to possess active antiperiodic properties, and was used to a considerable extent in the treatment of malarial fevers, but is falling into almost complete desuetude.

Capsicum.—The United States Pharmacopœia now recognizes only the small—less than an inch long—very fiery fruit of *Capsicum fastigiatum*, the African pepper, or *Chillies*. The large, bright red, conical or ovate, comparatively mild peppers of the market are from *C. annuum;* they are sometimes known as West India peppers. Capsicum (also called Cayenne pepper) contains as its active principle an exceedingly acrid oleoresin.

Capsicum is a very powerful local irritant, its oleoresin, when applied to the skin, producing in a very few minutes intense pain and redness, and finally destroying the cuticle. In the alimentary canal it acts in a similar manner: thus, moderate doses produce merely a pleasant feeling of warmth in the stomach, while overdoses may cause gastro-intestinal inflammation, with severe pain, as well as vomiting and purging, followed, after a time, by strangury and other evidences of genito-urinary irritation. The chief use of capsicum is as a condiment; yet it is often added with advantage to tonic pills to increase their immediate action on the stomach. When there is habitual feeble digestion, with flatulence, its free use on food may do good. In adynamic diseases, especially as occurring among drunkards, capsicum is often very useful by stimulating the stomach up to the point of digesting food. *Locally,* either as the diluted tincture in a gargle or applied in powder or tincture by means of a swab, it is useful in severe tonsillitis, especially in that accompanying scarlet fever.

EMETICS.

The act of vomiting is supposed to be controlled by a special center in the medulla. This center, however, differs in its pharmacological relations with most of the other medullary centers, so that the ordinary stimulants of the medulla generally do not give rise to emesis. Drugs may cause vomiting either by a direct stimulation of this center or reflexly by irritation of the gastric mucosa. The number of purely centrally acting emetics, however, has become more and more limited as further investigations of their mode of action have been made. Thus it has been found that the vomiting which follows the hypo-

dermic injection of antimony occurs simultaneously with the appearance of the substance in the stomach, which would indicate that the drug, being eliminated through the glands of the gastric mucous membrane, gives rise to an irritation of the stomach. It is probable, however, that with many emetics which are irritant to the stomach there is also more or less direct action upon the center. There is reason to believe that the sensation of nausea is largely dependent upon a centric effect of the drugs, for those substances, such as mustard, which act purely locally upon the mucous membrane of the stomach cause very much less persistent nausea.

In regard to the phenomena of vomiting, there are a few points which should be borne in mind. The first of these is the fact that

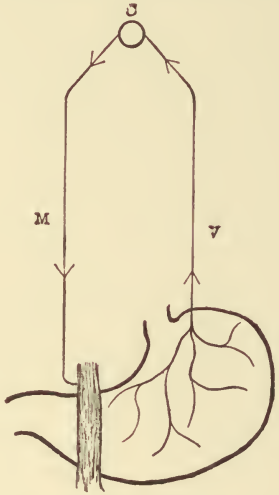

Fig. 24.—Diagram to show the mode of action of emetics. C., Vomiting center. V., Pneumogastric nerve conveying impulses from the stomach to the center. M., Motor nerve running to abdominal muscle. (For simplicity the other efferent nerves concerned in the act of vomiting are not represented.) Some drugs as zinc sulphate and mustard irritate the sensory nerves in the stomach and cause vomiting reflexly. Apomorphine acts directly on the vomiting center (C.). Ipecac and antimony probably act in both ways.

nausea is accompanied by a relaxation of the whole muscular apparatus, so that there is produced a marked feeling of weakness. At the same time there appears to be a dilatation of the peripheral blood-vessels, whether directly due to impulses sent out from the vomiting center or due to the forcing out of the blood from the abdominal areas by violent movements of the abdominal muscles is doubtful. Probably as a result of this determination of the blood toward the periphery there is an increase in the secretions, especially of the skin and bronchial tract.

Emetics are used for the following purposes:

(1) To empty the stomach of irritating or poisonous substances. It is not necessary to dwell upon the use of emetics in the treatment

of drug poisons, but merely to point out that where the purpose is to produce an expulsion of the gastric contents the mechanical emetics, which act very promptly and with less disturbance to the general system, are ordinarily to be preferred. Attention may also be called to the fact that many unexpected symptoms may be the result of the presence of irritant foodstuffs in the stomach, such as urticaria in adults and convulsions in children.

(2) To affect the portal circulation. Probably many of the symptoms which have been ascribed to biliousness are in reality due to the presence of undigested food in the stomach rather than to any absence of bile in the intestines, so that the relief which is obtained by emetics in these conditions is largely through the evacuation of the materies morbi rather than any effect upon the portal circulation. But the fact remains that during the act of vomiting there is a squeezing out of bile from the gall-bladder and biliary passages into the duodenum, and it will be remembered that the bile salts are powerful excitants to the secretion of bile by the liver. Moreover, the violent movements of the abdominal muscles mechanically press out blood from the abdominal circulation, especially of the liver, and in this way can relieve portal congestions. In catarrhal jaundice, emetics can do much good by causing the dislodgment of a mucous plug from the ducts, but when the retention of bile is due to the presence of a calculus the chances of forcing out the stone by external violence are probably no greater than those of lethal rupture of the gall-bladder.

(3) Emetics are sometimes used to dislodge foreign bodies from the respiratory passages. They were formerly employed for this purpose chiefly in treatment of membranous croup, but their use has been largely superseded by surgical measures.

(4) In small doses, emetics are used to increase the secretion of the bronchial glands (see Expectorants) and of the skin (see Diaphoretics).

Contra-indications.—Emetics should not be used where there is congestion of the brain, since during the act of vomiting the blood which is forced out of the abdomen will be partly driven into the cranial cavity. In advanced pregnancy and hernia, while not absolutely contra-indicated, they must be employed with great caution.

APOMORPHINE HYDROCHLORIDE.

Materia Medica.—Apomorphine, which was discovered by Matthieson and Wright, is made by dehydration of morphine, usually through the action of strong hydrochloric acid. It occurs as a snow-white powder, permanent when dry, but in solution, or when exposed to moisture, becoming green and finally almost black. There has been considerable discussion as to the properties of this green product; it seems, however, not to be poisonous, but to lose the characteristic activity of apomorphine.

Physiological Action.—The soluble salts of apomorphine, when

pure, are not irritant. They are absorbed with great rapidity, especially through the subcutaneous tissue. The vomiting which is purely of central origin is accompanied to a marked degree with nausea and the attendant phenomena, such as profuse salivation, increase in the secretion of the bronchial passages, free sweating, and muscular weakness. Small doses may produce the latter symptoms without the active occurrence of emesis.

In large doses, in the lower animals, apomorphine causes symptoms of excitement, followed by depression and weakness. Thus, in the dog, there is produced a condition of intense restlessness and evidences of excitement and terror, with later failing muscular strength, followed by rapid respiration and convulsions. The cause of the convulsions is not definitely known, but they are probably of cerebral origin. The muscular weakness appears to be due to an action upon the peripheral nerves. A number of clinicians have reported narcotic effects from morphine too small to produce emesis. It is possible that these effects have been due to impurities in the drug.

While fatal doses kill by the arrest of respiration, there appears to be a primary stimulation of the respiratory center. By toxic doses the heart is depressed, as well as the respiration.

Therapeutics.—Apomorphine is a safe and reliable emetic, and may be used whenever it is desired simply to empty the stomach. Apomorphine is a useful expectorant in acute bronchitis whenever it is desirable to increase the bronchial secretion. In the "drunk wards" of some of the Philadelphia hospitals for the relief of acute debauch apomorphine is preferred because the subjects habitually go to sleep directly after the vomiting ceases.

Probably because it has morphine in its name there was at one time a rather wide-spread belief that apomorphine was not a suitable emetic in narcotic poisoning. In fact, however, narcotics influence the action of apomorphine only as they do that of every other emetic, and if apomorphine has any narcotic influence it does not interfere with its emetic action. Apomorphine may, therefore, be used in any poisoning: hypodermically given, it is often especially useful as a reinforcement of a mechanical emetic exhibited by the mouth.

Administration.—As an emetic, apomorphine has usually been administered hypodermically, in doses of one-tenth of a grain (0.006 Gm.), repeated every ten minutes until some effect is induced; but it may be exhibited by the stomach in double the amount. In cases of severe poisoning, where time is of great moment, it may be well to give as much as one-fourth of a grain (0.016 Gm.) at a single injection. In children and feeble persons it should be employed always with caution, since, according to Harnack, the drug is very liable to produce collapse. The expectorant dose, for the adult, is from one-twentieth to one-fifteenth of a grain (0.003–0.004 Gm.).

IPECACUANHA.

Materia Medica.—The United States Pharmacopœia recognizes the roots of the *Cephælis ipecacuanha* (Rio ipecac) and *Cephælis acuminata* (Carthagena ipecac), small shrubs native in South America, but which have been cultivated successfully in the Straits Settlement, producing so-called Johore ipecac.

These roots are from one-eighth to one-fourth inch in diameter and four to eight inches long, brown or grayish in color, variously bent and contorted and marked on the surface with numerous prominent rings. The root itself has but very little odor, but when powdered has a dusty, peculiar smell and in some persons excites sneezing. The taste is bitter, acrid, and nauseous. They depend for their activity upon the presence of two alkaloids, *emetine* and *cephaëline*.* There is a third alkaloid, *psychotrine*, which is, however, almost inert. The Pharmacopœia requires that ipecac contain at least 1.7 per cent. of aggregate alkaloids.

Official Preparations:

Ipecacuanha	Emetic dose 30 grains (2 Gm.).
Emetinæ Hydrochloridum	¼ to ½ grain (0.03–0.06 Gm.).
Pulvis Ipecacuanhæ et Opii—Dover's Powder—(10 per cent.)	3 to 10 grains (0.2–0.6 Gm.).
Fluidextractum Ipecacuanhæ	Expectorant 1 to 5 minims (0.06–0.30 mil). Emetic 30 minims (2 mils).
Syrupus Ipecacuanhæ (7 per cent.)	5 to 20 minims (0.3–1.2 mils).

Physiological Action.—Locally ipecac is intensely irritant to mucous membranes, and sufficiently so to the skin that when applied by inunction it may cause pustulation. The vomiting it produces, however, according to the experiments of Hatcher, is due more to the effect upon the vomiting center than to this local irritant action. Emetine is an active amœbicide. According to Vedder, 1 part of emetine in 100,000, or 1 part of ipecac in 10,000, will kill the *Entamœba dysenteriæ*.

When taken by the stomach it is not possible to elicit much general action from a single dose of ipecac, because it is vomited before absorption takes place. When, however, it is injected subcutaneously or intravenously it has a marked effect upon the system, being depressant to the motor side of the spinal cord and probably also to the respiratory center. According to Levy and Rowntree, large doses of emetine are depressant to the heart, and even moderate quantities, if administered

* According to the experiments of Carl Lowin, emetine is only a feeble emetic, while cephaëline is a very powerful emetic. On the other hand, cephaëline does not act upon the lungs at all, so that the emetic influence of ipecacuanha is dependent upon the presence of cephaëline—its expectorant influence upon the presence of emetine.

continuously, may cause serious circulatory failure. A number of investigators have observed peculiar areas of pallor and of intense hyperæmia in the pulmonary tissue after the exhibition of emetine. This alkaloid seems to be largely eliminated through the mucous glands of the intestinal tract, and even when given intravenously it may cause violent enteritis.

THERAPEUTICS.—As an emetic, ipecac is rarely used when it is desirable simply to empty the stomach; its most frequent employment being in cases of portal congestion, because of the common belief that it exercises a direct influence upon the liver. As a nauseating or sedative expectorant in the early stages of acute bronchitis, preparations of ipecacuanha rank among our most valuable remedies. It is doubtful whether, as believed by some, this drug exercises any action upon the bronchial mucosa aside from its nauseating effect. It is probably also through this latter action that it increases the secretion of the sweat-glands. As a diaphoretic it is almost universally administered combined with opium in the form of the so-called Dover's powders.

Ipecac was originally introduced into medicine as an antidysenteric. For many years there was great difference of opinion as to whether the value of the drug in this disease was due to its alkaloids or to some other principle, and indeed it was even questioned whether the drug possessed any curative properties. We now know that its beneficial action is due chiefly, if not solely, to the alkaloid emetine. Since this alkaloid acts by destroying the amœba, and since neither it nor the whole drug possesses any marked bactericidal powers, it is evident that in cases of bacillary dysentery the ipecac treatment is useless.

One of the serious difficulties in the use of the drug has been that when given in sufficient doses to affect the entamœba it is likely to produce vomiting so promptly that much of the dose administered would be rejected before absorption. Recently this difficulty has been entirely overcome by the hypodermic use of the alkaloid emetine. The value of the latter, which is abundantly established, is doubtless due to an elimination through the glands of the intestines. The dose of emetine is ordinarily about one-third of a grain repeated from three to six times a day. Where this alkaloid is not available probably the best method of administration is to give the ipecac in pill form—preferably keratin coated—in doses of five grains every two hours, guarding against emesis, if necessary, by the use of opium. In other infections due to this parasite, as for instance in amœbic abscess of the liver, the emetine treatment is also of great value.

Ipecac has been credited with direct effects upon the liver and has consequently been recommended in various forms of biliousness, jaundice and hepatitis. Outside of those cases which are due to amœbic infections of the liver it is improbable that it possesses any virtues in this direction which cannot be ascribed to its emetic powers. Both the crude drug and the alkaloid emetine have been used with asserted benefit in the treatment of internal hemorrhages, especially from the lungs.

Because of its local irritant action in vomiting of reflex origin, such as occurs during pregnancy, the drug is frequently of service in small doses.

ANTIMONY.

Materia Medica.—The only salt of antimony recognized by the United States Pharmacopœia is the double tartrate of antimony and potassium, commonly known as tartar emetic. This occurs as transparent efflorescent crystals soluble in sixteen parts of water, with a taste at first very slight, but after a time styptic and acrid. It is incompatible with alkalies, with tannic acid, and the mineral acids.

Official Preparations:

Antimonii et Potassii Tartratis (Tartar Emetic)	{ Expectorant 1/30 grain (0.5 milligm.). Emetic ½ grain (0.03 Gm.).
Syrupus Scillæ Compositus (0.2 per cent.)	½ to 1 fluidrachm (2–4 mils).

Physiological Action.—Locally tartar emetic is an irritant, producing, if the contact be sufficiently prolonged, burning pain and pustulation; on susceptible skins this may follow in a short time, but generally prolonged application is required.

When taken in sufficient doses antimony causes emesis, which is accompanied with great nausea, muscular weakness, and relaxation of the system. The vomiting produced by tartar emetic seems to be the result chiefly of a local irritant action upon the walls of the stomach, for, although when injected into a vein it produces vomiting, this comes on simultaneously with the appearance of the metal in the gastric contents, it being eliminated through the glands of the stomach. The fact, however, that the drug is capable of producing emesis when the stomach has been removed and replaced by pig's bladder would indicate that it has also a central emetic action.

Antimony is a powerful depressant to the circulation. There is, after its administration, in proper dose, a marked slowing of the pulse with fall of the blood-pressure. This fall in pressure seems to be due chiefly to a direct depressant action upon the heart muscle, although there is some evidence that the vasomotor centers are also affected. In toxic quantities the drug produces progressive weakening of the cardiac force and the heart is arrested in diastole.

In large quantities antimony produces a lessening and, finally, total abolition of reflexes. Since it has been noted in the rabbit that voluntary movement may persist even after complete loss of reflex movement it is evident that the action must be upon the sensory system. After ligating the artery to one leg, thus preventing the access of the poison to one nerve, iritation of either the protected or poisoned leg will produce no reflex. It follows, therefore, that the drug is depressant to the sensory ganglia of the spinal cord. After large doses there is also a depression of the respiration.

Therapeutic Uses.—As an emetic antimony is to-day but rarely employed. The doses required to produce vomiting are large enough that if the emesis does not occur promptly sufficient of the drug may be absorbed to exercise an undesirable amount of depression on the circulation.

Like other nauseant substances, in small doses the tartar emetic increases the bronchial secretions, and is a useful remedy in the earlier stages of acute bronchitis. Because of its depressant influence upon the heart it should not be employed in young children nor in the aged, nor in persons with feeble circulation. It is to be reserved especially for robust patients, in whom it often acts most happily.

Antimony was formerly used for the purpose of quieting excitement of the heart and lowering arterial tension, especially in sthenic inflammations, such as the early stages of pneumonia. Its action as a cardiac sedative is essentially different from that of aconite and veratrum, for, whereas these drugs act upon the cardio-inhibitory mechanism, antimony is directly depressant to the heart muscle. It seems improbable that the weakening of the heart can serve any useful purpose, and the remedy has been almost completely abandoned.

Antimony has a powerful action in destroying the trypanosomes. Plimmer and Thomson have found that even with the tartrate of potassium and antimony the trypanosome could be made quickly to disappear from the blood of infected rats, although in considerable proportion of instances there was a recurrence of the infection. Of the various organic derivatives of antimony which have been brought forward as remedies for trypanosomiasis, only one, as far as my reading goes, has been used in human sleeping sickness with results which encourage further trial of it, the aniline-antimonial tartrate. Klemperer asserts that small doses of antimony administered subcutaneously are of value in pernicious anæmia.

Toxicology.—The symptoms of antimony poisoning are nausea, vomiting, great muscular relaxation, with a marked reduction of the force of the pulse and, in the early stages, also of its rate, the skin is bedewed with sweat, and the saliva is often also increased. The vomiting is violent, repeated, and often accompanied by burning pain over the œsophagus and stomach. If the dose of the poison has been large there is frequently free serous purging, the discharges sometimes resembling those of cholera, or, in some cases, becoming bloody. Partly because of the large amount of water lost through the vomiting and purging, and partly because of the depressant action upon the heart, the pulse becomes almost or completely impalpable. As the poisoning progresses the symptoms of collapse become more profound; there is a pinched expression to the face, cyanotic pallor, profuse cold sweats, fall of the bodily temperature and usually stupor, and sometimes convulsions, before death. In some cases there is also evidence of irritation of the kidney, shown at times by increased diuresis and at others by scanty albuminous and even bloody urine.

The symptoms of antimony poisoning so closely resemble those of cholera and of arsenic poisoning that in the absence of definite history a positive diagnosis can usually be made only by chemical examination. In any suspected case of poisoning the physician should, therefore, save the urine for chemical examination. After death there are found the lesions of gastro-intestinal and of renal irritation.

The treatment of antimony poisoning consists in washing out the alimentary canal with large draughts of tannic acid—the best known antidote—the free administration of opium by the mouth, or, if it be not retained, morphine hypodermically, the use of strychnine, atropine, and digitalis to maintain respiration and circulation, and the external application of heat. If the purgation has been severe the hypodermic or intravenous injection of physiological salt solution may be useful to replace the lost fluid; the quantity, however, should not be too large, lest too great a strain be put upon the weakened heart.

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CATHARTICS.

Cathartics may act either by increasing the amount of fluid in the bowel or by increasing the activity of the intestinal peristalsis. The contents of the small intestine are poured out through the ileocæcal valve in an almost fluid condition and so continuously that it has been called a normal diarrhœa; the inspissation and formation of the fecal masses take place during the comparatively long sojourn in the colon. It is therefore evident that a drug which merely increases the movements of the muscles of the large bowel may give rise to copious watery movements. The mechanism of purgation differs so greatly with different classes of drugs that it will be considered under the different groups.

Cathartics are used for the following purposes:

1. *To Empty the Bowels.*—The cathartics are used not only to evacuate the ordinary fecal matters in constipation, but to remove foreign offending materials, as indigestible or irritant foods, bacteria, intestinal parasites, or poisons.

2. *To Evacuate Dropsical Effusions.*—Certain cathartics cause a marked increase in the watery constituents of the intestinal contents, and this fluid must be drawn from the surrounding blood-vessels, which in turn are filled up from the subcutaneous fluids. In this manner large amounts of water may be rapidly eliminated from the system. Purgation is probably the most efficacious method of relief in general dropsy, but is also the most exhausting, and due regard must be had for the strength of the patient before instituting this line of treatment.

3. *To Eliminate.*—It cannot be doubted that the use of purgatives in such diseases as fevers and cholera, with the idea of eliminating some *materies morbi,* rests simply upon a crude, unproved, and probably false pathology. In rheumatic disease and in gout it is more probable that they do good in this way, although it is by no means certain that the advantage derived from their use is not simply due to depletion. In cases of retained renal secretion, the evidence is very decided that they do aid in expelling the products of retrograde metamorphosis.

4. *To Influence the Portal Circulation.*—Those cathartics which increase the peristaltic movements seem mechanically to cause the pouring out of the bile into the intestines. The relief, however, which is caused by these drugs in cases of so-called biliousness, or congestion of the liver, is probably due more to the influence, upon the abdominal circulation, of the determination of fluid towards the bowel. The question of the action of cathartics upon the liver will be taken up in more detail in connection with the mercurials.

The presence of bile in the intestinal tract is apparently necessary for the action of certain cathartics, especially the vegetable laxatives. Whether it acts by increasing the solubility of the cathartic principles or in some other unknown way is as yet uncertain.

Classification.—The purgatives are sometimes divided, according to the severity of their effects, into laxatives, purgatives, and drastics. As the difference between these classes is, however, largely a question of dosage, and takes no cognizance of certain well-marked pharmacological relations, which are also of therapeutic importance, the following division, based upon their chemical relations, seems not only scientific but more practically useful:

(1) Purgatives containing *derivatives of anthraquinone* *—rhubarb, senna, cascara sagrada, frangula, and aloes.

(2) Vegetable cathartics *containing resinous glucosides and acids*—this includes most of the so-called drastics, as jalap, podophyllin, colocynth, scammony, and gamboge.

(3) *Cathartic oils*—castor oil, croton oil.

(4) *Salines*—the salts of sulphuric, phosphoric, citric, and tartaric acids.

(5) *Phenolphthalein.*

(6) *Mercurials,* considered elsewhere (see p. 303).

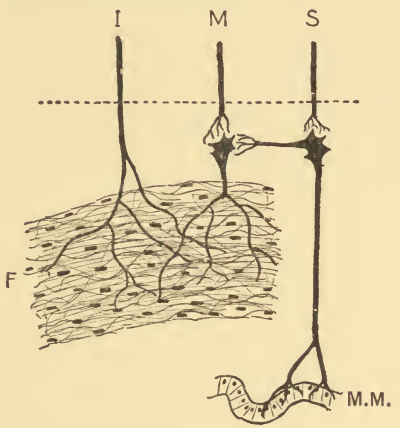


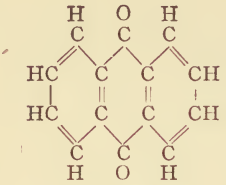
Fig. 25.—Diagram to show how cathartics influence intestinal movements. M M, Mucous membrane. S, Sensory nerve. M, Motor nerve. I, Inhibitory nerve. F, Muscular fibres. The structures between the dotted line and the muscular layer constitute Auerbach's plexus. The vegetable purgatives irritate the terminations of the sensory nerves, reflexly increasing peristalsis.

ANTHRAQUINONE GROUP.

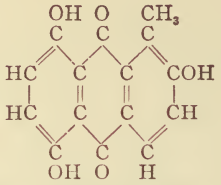
A number of vegetable laxatives contain derivatives of anthraquinone, to which they owe, at least in part, their laxative properties. Among these principles the most important, which have so far been isolated, are emodin—trioxymethyl-anthraquinone—and chrysophanic acid—dioxymethyl-anthraquinone [$C_{14}H_5(CH_3)(OH)_2O_2$]. The most prominent plants containing anthraquinone derivatives are rhubarb, senna, aloes, cascara sagrada, and frangula. It is to be noted, how-

* These are also spoken of as the anthracene derivatives because anthraquinone is itself derived from anthracene.

ever, that these plants appear to contain other bodies which aid their aperient properties, and that the pure principles are frequently less purgative than crude drug, perhaps for purely physical reasons.



Anthraquinone.



Trioxymethyl-anthraquinone (Emodin).

The anthraquinone derivatives seem to cause catharsis by a direct irritant influence upon the intestines, leading thereby, perhaps, to some increase in the secretion of the intestinal fluids, but chiefly hastening peristalsis. According to the recent investigations of Magnus, the effect of this group of drugs is principally upon the large bowel. Although none of this group of remedies are sufficiently actively irritant to give rise to the severe inflammation which may be caused by the second group of cathartics, their local effects upon the bowel forbid their use in conditions of enteric inflammations. They are used when it is desired simply to empty the colon, and especially in chronic constipation.

ALOES.

Aloes appears to have been first produced in the Island of Socotra as far back as the time of Alexander the Great, 333 B. C. Several species of the genus *Aloe* yield a purgative juice, and at present the U. S. Pharmacopœia recognizes three varieties. Socotrine aloes is derived from the *Aloe Perryi* and comes from the Island of Socotra off the east coast of Africa. Curaçao aloes from the *A. vera,* which is the most common variety in this country, is grown in several of the West Indian islands. It is known also as Barbadoes aloes, but at present little is produced in the latter island. Cape aloes, from the *A. ferox,* is grown at the Cape of Good Hope.

Aloes is obtained by cutting off the thick, succulent leaves of various species of the genus *Aloe* allowing the juice to drain into skins, troughs, or other vessels, and afterwards inspissating either by exposure to the sun or by means of artificial heat. The drug is blackish-brown or yellowish-brown, of a bitter, nauseous taste, often with a smooth fracture, and in the best varieties with garnetty edges; it yields its virtues to alcohol, imperfectly to water, and very imperfectly to alkaline solutions.

The activity of aloes is due to the presence of a crystalline principle known as aloin, which yields, on decomposition, emodin. Aloin

is neutral, odorless, of a taste at first sweetish, afterwards intensely bitter; is soluble with difficulty in cold water, freely in boiling water and in alcohol. There are three varieties of aloin—*barbaloin, socaloin,* and *nataloin,* obtained respectively from the Barbadoes, the Socotrine, and the Cape aloes. Although there appears to be considerable difference in the activity of the various aloins, the present Pharmacopœia recognizes no distinction between them.

Official Preparations:

Aloe .....4 to 10 grains (0.3–0.6 Gm.).
Aloinum .....⅛ to ½ grain (0.01–0.03 Gm.).
Extractum Aloes .....1 to 3 grains (0.06–0.2 Gm.).
Pilulæ Aloes (2 grains).....2 to 4 pills.
Tinctura Aloes (10 per cent.).....1 to 3 fluidrachms (4–12 mils).

RHAMNUS.

Two species of the genus *Rhamnus* are recognized by the United States Pharmacopœia, the *Rhamnus frangula* (the buckthorn) and the *Rhamnus purshiana* (the California buckthorn), under the names, respectively, of Frangula and Cascara sagrada. The former is, however, but little used in this country.

The California buckthorn is a small tree which is found on the Pacific coast from California to Oregon. The official portion of the plant is the bark, which is commonly known as *cascara sagrada.* This is from $^1/_{16}$ to ⅛ of an inch thick, and occurs in the market in the form of quills from two to four inches long; the outer surface is gray, the inner brown. The taste is bitter and nauseous. The purgative activity of cascara is due to a glucoside, known as purshianin or cascarin, which yields, on decomposition, emodin. It also contains a bitter principle which is believed by some to exercise a tonic action upon the intestinal muscles. The bark should not be used until at least one year after collection, as when fresh it contains an irritant ferment, and is likely to cause much griping.

Official Preparations:

Extractum Cascaræ Sagradæ.....2 to 5 grains (0.12–0.3 Gm.).
Fluidextractum Cascaræ Sagradæ.....½ to 2 fluidrachms (2–8 mils).
Fluidextractum Cascaræ Sagradæ Aromaticum½ to 2 fluidrachms (2–8 mils).
Fluidextractum Frangulæ .....15 minims (1 mil).

RHUBARB.

The dried rhizome of *Rheum officinale* (Baillon) and other species of rheum growing in China and Thibet.

The rhubarbs are large perennial herbs with leaves two to four feet long, the leaves of one species being used in this country as a foodstuff.

Rhubarb occurs in hard, irregularly cylindrical or roundish bits, of a brownish-yellow color, with a pleasant aromatic odor and a peculiar bitter taste, imparting to the teeth a sense of grittiness, due to the presence of a number of minute crystals of calcium oxalate.

It contains, besides *emodin,* a glucoside, *chrysophan,* which yields, on decomposition, *chrysophanic acid.* There is also present a notable proportion of tannin. Because of its comparatively large amount of tannic acid, rhubarb is very liable to produce constipation following its purgative effect.

Official Preparations:

Extractum Rhei .....5 to 10 grains (0.3–0.6 Gm.).
Pilulæ Rhei Compositæ (Each 2 grains Rhubarb and 1½ grains Aloes).
Pulvis Rhei Compositus (Rhubarb 25 per cent., with Magnesium Oxide and Ginger).½ to 1 drachm (2–4 Gm.).
Fluidextractum Rhei .....15 to 30 minims (1–2 mils).
Tinctura Rhei (20 per cent.).....1 to 2 fluidrachms (4–8 mils).
Tinctura Rhei Aromatica (20 per cent.).....1 to 2 fluidrachms (4–8 mils).
Syrupus Rhei (10 per cent.).....2 fluidrachms (8 mils).
Syrupus Rhei Aromaticus (3 per cent.).....4 fluidrachms (15 mils).

SENNA.

Under the name of Senna various species of the genus *Cassia* have found their way into commerce, but at present the United States Pharmacopœia recognizes only the leaflets of the *Cassia acutifolia* of Nubia and Upper Egypt (Alexandria senna), and of the *Cassia angustifolia* of Southern India (Tinnevelly senna). The senna leaves vary from three-fourths of an inch to an inch and a half in length, and are to be distinguished by the inequality of their bases, the two sides of the lamina or leaf-blade joining the midrib at unequal heights and angles. Alexandria senna is characterized by the presence of the shorter argel-leaves, with equal bases, by the ovate-pointed leaflet. India senna is distinguished by the oblong leaflets, from one to two inches in length, entire and perfect. Owing probably to the fact that it is largely cultivated in the southern portion of the peninsula of Hindostan, especially near Tinnevelly, this senna at present constitutes the greater part of that which is sold in the drugstores. Its purgative powers are due to the presence of chrysophan and cathartic acid.

Official Preparations:

Pulvis Glycyrrhizæ Compositus (18 per cent.)½ to 2 drachms (2–8 Gm.).
Fluidextractum Sennæ .....½ to 1 fluidrachm (2–4 Gm.).
Syrupus Sennæ (25 per cent.) .....1–4 fluidrachms (4–15 mils).
Infusum Sennæ Compositum (Black Draught) (6 per cent.).....4–6 fluidounces (120–180 mils).

Therapeutics.—Because their effect is chiefly upon the intestinal muscles, the vegetable purgatives are chiefly used in those atonic conditions of the bowel which are associated with chronic constipation. Very commonly a preference in chronic cases is expressed for cascara

sagrada, but both aloes and senna are useful drugs for this purpose. Because of their local irritant effect upon the intestinal mucous membrane, this class of remedies should be avoided in all conditions in which there is inflammation or irritation of the alimentary tract.

On account of the comparative slowness of their action—eight to ten hours—they are generally not serviceable in acute constipation.

In enteritis, for the purpose of evacuating the irritating substance, not only because of their own irritating effects upon the bowel but also because their action is limited largely to the lower bowel, they are not nearly so useful as the inorganic cathartics, and, although rhubarb is frequently employed for this purpose, in the opinion of the writer it is not a good practice. Rhubarb is also used to a considerable extent for its tannin content in cases of serous diarrhœa.

RESINOUS CATHARTICS.

In the second group of cathartics are included a number of vegetable drugs which contain irritant resins whose activity is due to the presence of various principles more or less closely related and mostly glucosidal in nature. These substances, probably by local irritant effect, increase the peristalsis and also the secretion of fluids. They give rise to a condition which has been justly likened to a true catarrh of the intestines. In overdose they are capable of setting up a gastro-enteritis sufficiently violent to threaten life.

Therapeutic Uses.—The cathartics of this group constitute what was formerly known as the drastics, and are generally too severe in their effects to be used alone. They are employed, first place, in very obstinate cases of chronic constipation to enhance the activity of the anthraquinone purgatives; and, second, they are used to evacuate dropsical fluids. Although very efficient for this purpose, they are so harsh in their action that to-day they are less frequently employed than the salines; but jalap and elaterine are still used to a considerable extent. The presence of bile in the intestines seems to be essential for the action of many, if not all, of this group of cathartics.

JALAP.

The roots of a number of plants of the family *Convolvulaceæ*—to which belongs the common morning-glory—contain irritant resins and hence act as cathartics. Of these plants the U. S. Pharmacopœia recognizes two, Jalap and Scammony. Of the unofficial drugs of this group, the most important is the so-called male jalap derived from the *Ipomœa orizabensis*.

Jalap is the tuberous root of *Exogonium purga*, a convolvulaceous vine growing in Mexico. Jalap comes into the market in two forms: one, that of the younger roots, which is sold undivided; the other, that of the old roots, which is brought into the market in transverse or longitudinal slices and in pieces. The first variety consists of very

hard, irregularly globular, brittle roots, about the size of a fist, or smaller, and often slashed with vertical incisions, made for the purpose of facilitating drying. Jalap contains a resinous glucoside, *convolvulin,* and a smaller quantity of another resin which appears to be identical with *scammonin.* The Pharmacopœia requires that it contain not less than 7 per cent. of resin.

Official Preparations:

Jalapa .....10 to 20 grains (0.6–1.3 Gm.).
Resina Jalapæ .....2 to 4 grains (0.12–0.25 Gm.).
Pulvis Jalapæ Compositus (Jalap 35, Potassium Bitartrate 65).....½ to 1 drachm (2–4 Gm.).

Therapeutics.—Jalap is an efficient, but harshly acting, cathartic, producing large, watery stools. It is, at present, rarely used except for the evacuation of fluid from the body in the treatment of ascites and other forms of dropsy. It is frequently combined with the saline cathartics, although the proportion of potassium bitartrate in the official compound powder of jalap is too small.

SCAMMONY.

The root of the *Convolvulus scammonia,* a Syrian vine, contains about 8 per cent. of resins, to which it owes its cathartic properties. Formerly the resin was collected by incising living roots and collecting the exudate; this mixture of gum and resin was recognized in the U. S. Pharmacopœia VIII, under the name of "scammonium," but the present Pharmacopœia recognizes only the root itself (*Scammonii radix*) and the resin extracted by percolation with alcohol. Scammony root is almost never used in the crude form. The active principle of scammony is a resinous substance known as *scammonin,* which is believed to be identical with *jalapin,* obtained from the male jalap (*Ipomœa orizabensis*) and closely allied to the *convolvulin* of true jalap.

Official Preparations:

Resina Scammonii .....2 to 5 grains (0.13 to 0.3 Gm.).
Extractum Colocynthidis Compositum .....1 to 3 grains (0.06 to 0.2 Gm.).

Scammony is a harsh, active purgative, but it is little used except in the forms of the compound extract of colocynth and the compound cathartic pill, of which it is an ingredient.

COLOCYNTH.

This is the dried pulp of the fruit of *Citrullus colocynthis,* or bitter cucumber, a vine growing in South Africa, Japan, Syria, Egypt, Turkey, the islands of the Grecian Archipelago, etc. The fruit is a round gourd, from two to four inches in diameter, of a whitish or pale yellow color. It occurs in the market with or without its rind.

The pulp is dry and membranous, whitish, and contains the actively purgative glucoside *colocynthin,* first discovered by Herberger.

Official Preparations:

Extractum Colocynthidis .....3 to 5 grains (0.2–0.3 Gm.).
Extractum Colocynthidis Compositum (Extract of Colocynth 16, Purified Aloes 50, Resin of Scammony 14, Cardamom 6, Soap 14).....1 to 3 grains (0.06–0.2 Gm.).
Pilulæ Catharticæ Compositæ (each pill contains Compound Extract of Colocynth 0.08 Gm., Calomel 0.06 Gm., Resin of Jalap 0.02 Gm., Gamboge 0.015 Gm.).....1 to 3 pills.

Colocynth might well be omitted from our armamentarium with no great loss.

PODOPHYLLUM.

The rhizome of *Podophyllum peltatum,* or May-apple, a perennial herb, growing in the Northern and Middle United States. Podophyllum occurs in simple or branched, cylindrical, brownish pieces, about the thickness of a goose-quill, smooth or wrinkled longitudinally, often obscurely marked with the scars of leaf-scales, and furnished with numerous rootlets or their remnants attached to the lower surface. The taste is bitterish, acrid, and nauseous. The rhizome contains the alkaloid *berberine,* but the purgative power resides chiefly in *podophyllotoxin,* although it is probable that there are other purgative substances in the rhizome, especially an uncrystallizable resin, *podophylloresin.*

Official Preparations:

Resina Podophylli .....$^1/_{12}$ to $^1/_6$ grain (0.005–0.01 Gm.).
Fluidextractum Podophylli .....8 minims (0.5 mil).

Podophyllum was supposed by the eclectic practitioners to exercise an effect upon the liver, and was sometimes spoken of as the "vegetable mercury." It is extremely doubtful, however, whether it increases the amount of bile in the intestines any more than any other powerful cathartic. Its most important use is in the treatment of chronic constipation in combination with aloes or cascara.

GAMBOGE.

A gum resin, obtained in Siam by breaking off the leaves and young shoots of the tree known as *Garcinia hanburii* and catching in suitable vessels the juice as it drops. When the receptacles consist of hollow bamboos, the juice hardens into cylindrical casts, striated externally, and with a central cavity due to the loss of substance.

This is the so-called *pipe gamboge*. *Gamboge in sorts* occurs in irregular masses. Gamboge is a hard, resinoid substance, of a brittle, often conchoidal, fracture, of a deep reddish-orange color on exposed surfaces, more yellowish when freshly broken, affording a bright yellow powder, insoluble in water, with which it forms, however, an intensely yellow emulsion. It has little or no taste, but when chewed produces, after a time, an acrid sensation in the fauces.

ELATERIUM.

A substance deposited by the juice of the fruit of *Ecballium elaterium*, or squirting cucumber, a native of Greece, but cultivated in England. In the interior of the ovate fruit is an elastic sac, which contains the seeds, and at ripening becomes so distended with juice that when the fruit falls off the vine, and the support is removed from the stem end, a rupture occurs at the latter position, and the liquid with the seeds is forcibly projected. The medicinal principle is said to be contained only in this inner juice. In order to avoid loss, the fruit is picked with a piece of the stalk adherent to it before ripening, and is opened by slicing. *Elaterium* occurs in light, friable, slightly incurved, greenish-gray cakes about a line thick. The taste is acrid and bitter, the fracture finely granular. Owing to the variability of commercial elaterium, the United States Pharmacopœia now recognizes only the active principle, *Elaterin* (Elaterinum, U. S.), which was first separated in a pure state by Morries. It crystallizes in colorless, shining, rhombic, six-sided, odorless tables, of a very bitter sharp taste and neutral reaction.

According to Powers and Moore, elaterin is a mixture of two optical isomers, one of which is lævorotary and the other dextrorotary, and that the latter only is physiologically active. Both of these substances are crystalline. They are not glucosidal.

Official Preparations:

Elaterinum .....1/20 to 1/10 grain (3–5 Milligm.).
Trituratio Elaterini (10 per cent.).....½ grain (0.03 Gm.).

Physiological Action.—Locally applied, elaterium is a very decided irritant, producing, according to Pereira, ulcerations in the fingers of those who handle the fruit and prepare the drug for market. When taken internally, it acts on man as a most powerful hydragogue cathartic.

Kohler has proved that in animals elaterium is absorbed, even when given by the mouth, since he found it in the urine of poisoned dogs and rabbits.

Therapeutics.—Elaterium is certainly a most efficient hydragogue cathartic, producing, in properly regulated doses, the freest evacuations with comparatively little pain and irritation, and is much used in the treatment of general dropsy or ascites. As, however, its action is very exhausting, great care should be exercised not to give it in

too large doses, and also to support the strength of the patient during the period of purgation, and afterwards, by alcoholic stimulants, easily digested nutritious food and appropriate hygienic measures. In the latter stages of dropsy the injudicious use of elaterium may cause a fatal exhaustion. For the asserted power of elaterium in increasing the intestinal elimination of urea we have been unable to find authority. Clinical experience has, however, demonstrated the value of elaterium in uræmia. In order to deplete, elaterium has been employed in various diseases; but this use is not to be encouraged, and especially when there is any gastro-intestinal irritation or inflammation are the salines much preferable to elaterium.

Elaterium is without doubt capable of destroying life, but I know of but one recorded death—that of a woman in whom two and two-fifths grains of the extract of elaterium and sixteen grains of rhubarb caused uncontrollable vomiting and purging, ending in a fatal gastro-enteritis.

CATHARTIC OILS.

Although ordinary oleic acid appears to be mildly irritant to mucous membranes and therefore feebly laxative, certain closely allied fatty acids are powerfully cathartic. The two most important substances of this group are ricinoleic acid, from castor oil, and crotonoleic acid, from croton oil. It should be pointed out that the oils themselves are not irritant; that the irritant properties are only developed when they contain free acid. Croton oil, however, as it appears upon the market, generally contains free crotonoleic acid, and the commercial croton oil is therefore intensely irritant. Castor oil, on the other hand, may be obtained in which there is no free acid, and is a soothing and bland application like any other fixed oil.

When these oils reach the intestines they are split up, liberating their peculiar acids, which, acting as irritants, stimulate the peristalsis, affecting especially the small intestine.

CASTOR OIL.

A fixed, nearly odorless oil, of a nauseous taste, obtained from the seeds of *Ricinus communis,* a shrub native to India, by expression. The seeds are slightly warmed before being put under pressure, so as to liquefy their contained oil; and the crude oil obtained from them is boiled with a small amount of water, so as to coagulate its albuminous impurities. Castor oil is remarkable for being soluble not only in ether, but also in alcohol. The *castor-oil seeds,* or *beans,* as they are commonly called, contain an acrid, violently poisonous principle, *ricin.**

Oleum Ricini.....½ to 1 fluidounce (15–30 mils).

Ricin, while of no therapeutic importance, is interesting because

* Three beans have caused death in the adult. The symptoms, which do not usually come on until from two to five hours, are severe abdominal pain, violent vomiting and purging, which after a time may become bloody, collapse, severe

it acts on the system very similarly to the bacterial toxins. Indeed, much of our knowledge concerning the processes of immunity has been derived from studies made with ricin.

Therapeutics.—Because of a belief that castor oil would exercise a soothing effect upon the mucous membranes, due to its oleaginous nature, it has been largely used in the treatment of various forms of diarrhœa and enteritis, especially in children. As, however, it is decomposed by the fat-splitting ferments of the intestinal canal, liberating the irritant ricinoleic, it will act upon the intestine as an irritant rather than a sedative. The beneficial results which have followed its use in these conditions depend simply upon its cathartic effect, mechanically sweeping out the irritant. It differs in this connection from the first group of vegetable cathartics in the fact that it excites the small intestines, which is the usual location of the trouble. It appears to evacuate the bowel more thoroughly than will any other cathartic do without excessive irritation. The constipation which follows the use of castor oil is probably owing simply to the fact that it thoroughly empties the whole canal.

The unpleasant flavor of the oil may usually be covered by combining it with equal parts of glycerine, and flavoring with a highly aromatic volatile oil.

CROTON OIL.

The fixed oil obtained from the seeds of *Croton tiglium,* a euphorbiaceous shrub of Hindostan and other portions of Southern Asia, is official under the name of *Oleum tiglii.* This oil is quite viscid, varies in color from a pale yellow to a dark reddish brown, and has an acid reaction. Its taste is hot, acrid, and extremely persistent; its odor faint, but peculiar. Croton oil consists chiefly of the glycerites of ordinary fatty acids, but contains also *crotonoleic acid,* which has been supposed to be a pure principle, but is stated by Dunstan and Boole to be a mixture of inactive oil acids with a powerfully vesicating, resinous substance, *croton-resin.*

Therapeutics.—Locally applied, croton oil is an intense irritant, producing upon the skin an eruption which is at first papular but in a very short time becomes pustular. Croton oil is used chiefly where very violent or revulsant effect is desired, or in cases where the patient is unable to swallow, as in uræmia and eclampsia, in which case it may simply be dropped upon the tongue. Under ordinary circumstances, however, it is better to give it in the form of an emulsion, so as to avoid undue irritation of the upper part of the alimentary canal. Because it contains, generally, free crotonoleic acid, croton oil

muscular cramps, cold sweating skin, contracted features, thirst, restlessness, and small rapid pulse. After death, intense redness and even abrasion of the stomach and of the small intestine are found. After the stomach and large intestine have been thoroughly washed out with warm water, the treatment of castor bean poisoning is that of toxic gastro-enteritis,—namely, the use of opium, leeches, ice, demulcent drinks, counter-irritation, etc. See Kobert and Stillmark (*Arbeiten Pharmak. Inst. zu Dorpat,* iii).

often irritates the stomach, producing vomiting, and also acts much more promptly than does castor oil.

Toxicology.—Although in small amounts croton oil causes such severe symptoms, yet in larger quantities it has failed to produce as serious results as would be naturally expected. But there are recorded a number of fatal intoxications from large doses of the drug.

The treatment of croton-oil poisoning is purely symptomatic. Opium should be given to lessen the purging, demulcent drinks to lessen the irritation. If collapse develops, cardiac stimulants should be administered hypodermically and bodily temperature maintained by the application of external heat.

SALINE CATHARTICS.

Under the term of salines are included certain salts of the earthy metals, which, because of their slight absorbability from the intestinal tract, disturb the osmotic balance between the bowel contents and the surrounding tissues. In the majority of instances the ion determining the cathartic action is the acid radical, although certain bases, notably magnesium, seem to possess cathartic properties. The laxative salts are those of sulphuric, phosphoric, citric, and tartaric acids. The official salts of this class are: sodium sulphate, phosphate, and citrate; magnesium sulphate and citrate; sodium and potassium tartrate; potassium citrate and potassium bitartrate.*

The presence of one of these salts in the intestines, because it does not easily pass through the intestinal wall, not only prevents the absorption of water from the intestine but also encourages the passage of water from the surrounding tissues into the bowel by osmosis. It does not seem likely, however, that the pouring of fluid into the intestinal tract is the result solely of osmotic pressure, but that it is also dependent on a true stimulant influence on the intestinal glands. The investigations of Matthew Hay, although carried out many years ago, still remain the most probable expression of the mode of action of the saline cathartics. This author concluded that: (1) A saline purgative always excites more or less secretion in the intestines due to bitterness and specific properties of the salt rather than to osmosis; (2) the low diffusibility of the salt impedes the absorption of fluid; (3) between stimulated secretion on one hand, and lessened absorption on the other, there is an accumulation of fluid in the bowel; (4) the accumulated fluid, partly from ordinary dynamic laws, partly from a gentle stimulation of peristalsis, reaches the rectum and produces purgation.

While there is some diversity of opinion as to which one of the factors involved in the catharsis is the most important, so far as the practical utilities of this group are concerned there is almost complete

* The natural laxative waters, as those of Carlsbad, Saratoga, Vichy, Kissingen, etc., are simply mixtures of these drugs with other salts, usually including large quantities of sodium chloride. (Formulæ for making these salts are in the National Formulary.)

unanimity. The peculiar usefulness of the salines lies in their rapidity of action, their freedom from irritant properties, and the liquid character of the stools produced.

Official Saline Cathartics:

Magnesii Sulphas [Epsom Salts].....4 drachms (15 Gm.).
Magnesii Sulphas Effervescens (50 per cent.) .....1 ounce (30 Gm.).
Sodii Sulphas [Glauber's Salt].....4 drachms (15 Gm.).
Sodii Phosphas .....1 to 2 drachms (4–8 Gm.).
Sodii Phosphas Effervescens (20 per cent.)..4 drachms (15 Gm.).
Sodii Phosphas Exsiccatus.....½ drachm (2 Gm.).
Potassii et Sodii Tartras [Rochelle Salt]....2 to 4 drachms (8–15 Gm.).
Potassii Bitartras [Cream of Tartar].....½ to 1 drachm (2–4 Gm.).
Pulvis Effervescens Compositus [Seidlitz Powder] .....1 pair of powders.
Potassii Citras.....15 to 45 grains (1–3 Gm.).
Potassii Citras Effervescens (20 per cent.)...1 drachm (4 Gm.).
Liquor Potassii Citratis (8 per cent.).....½ to 1 fluidounce (15–30 mils).
Liquor Magnesii Citratis.....4 to 8 fluidounces (120–240 mils).

Sodium sulphate (Glauber's salt) occurs in six-sided, very efflorescent, striated prisms, which finally crumble into a white powder. It acts like magnesium sulphate, but is more powerful; it is, however, little used on account of its extremely nauseous taste. It is the chief active principle of many natural purgative waters which are so useful in chronic gastric and other abdominal catarrhs with constipation.

Sodium phosphate, the disodium hydrogen phosphate (Na_2HPO_4), occurs in colorless, transparent crystals, which effloresce and become opaque on exposure. It is soluble in 5.5 parts of water, and has a saline taste, closely resembling that of common salt. In large doses it is a mild saline purgative, but as such is not at present very much employed for this purpose. By many it is supposed to have a specific action on the liver and is widely used in chronic constipation associated with hepatic torpor. It is also frequently employed in lithæmic disorders.

Potassium and sodium tartrate, or Rochelle salt, is made by adding sodium carbonate to solution of potassium bitartrate. It is soluble in 1.2 parts of water, and has a saline taste much less disagreeable than sulphates. It is, however, more mild, and decidedly less efficient in its action.

The most agreeable means of administering this salt is in the form of the *Seidlitz powder* (*Pulvis effervescens compositus*). This comes in two packets; the white paper contains thirty-five grains of tartaric acid, the blue paper forty grains of sodium bicarbonate and two

*Acid sodium phosphate (NaH_2PO_4) is used to acidulate the urine in doses of from 15 to 20 grains every three or four hours until the effect is produced. It may be extemporized by adding eighty parts of the official sodium phosphate to two hundred parts of the official dilute phosphoric acid.

drachms of Rochelle salt. When they are taken, the powders are dissolved separately, the solutions added, and the whole drunk while effervescing. One pair of powders is the usual dose; but not rarely even two pair will fail to purge.

CITRIC ACID.

Citric acid is the acid of lemon- and lime-juice. It occurs in rhomboidal prisms, of a sour, almost corrosive, taste, freely soluble in water. Lemon-juice contains from seven to nine per cent. of citric acid; it was formerly official, but was dropped in the last revision of the Pharmacopœia.

Official Preparations:

Syrupus Acidi Citrici (1 per cent.).....Used as a vehicle.
Liquor Magnesii Citratis.....8 fluidounces (240 mils).
Potassii Citras .....20 to 30 grains (1.3–2.0 Gm.).
Liquor Potassii Citratis (8 per cent.).....½ to 1 fluidounce (15–30 mils).
Sodii Citras .....15 to 30 grains (1–2 Gm.).

Therapeutics.—*Lemon-juice* is a valuable remedy, but how or why it acts is at present entirely unknown. Neither citric acid nor any of its known salts act in disease as does the juice of the fruit. The chief and most important use of lemon-juice is in the cure and prevention of scurvy. During the disease three or four ounces may be given three times a day. As a prophylactic against the disease, lemon-juice is simply invaluable; but it is absolutely necessary that it be of good quality. In catarrhal jaundice and in habitual torpor of the liver the free administration of lemon-juice often aids in effecting a cure. In fevers, lemonade is a refreshing and useful refrigerant drink.

Both potassium and sodium citrate are oxidized into carbonates in the system and therefore exercise an alkalizing effect.

Sodium citrate has been extensively used in infant feeding to prevent the formation of hard curds in cow's milk. This action is due to the fact that citric acid prevents in a large measure the ionic action of calcium, the curd which is formed being composed of a sodium caseinate, which is much softer than the calcium combination.

The salts of citric acid are useful as saline diuretics (see p. 29). They are also, when given in large doses, mildly laxative. The effervescent potassium citrate contains also sodium tartrate and is therefore more actively cathartic than the plain salt.

Sodium citrate has been recommended by Wright as a local application in the treatment of furunculosis. A piece of cotton saturated with a solution containing two grains of sodium citrate and twenty grains of sodium chloride to the ounce of water is placed over the furuncle and covered with an impermeable dressing.

MAGNESIUM.

Materia Medica.—The United States Pharmacopœia recognizes the carbonate, two forms of the oxide, the sulphate, and the citrate of magnesium. *Magnesium carbonate* is manufactured by precipitating

a solution of magnesium sulphate by one of sodium carbonate. If the two solutions be concentrated, the dense or heavy carbonate will fall; on the other hand, if the solutions be dilute, the precipitate will be a light carbonate. Heavy magnesia is obtained by calcining a heavy carbonate; light magnesia, by using a light carbonate. All of these substances are of a milk-white color, and occur in powder; the carbonates sometimes in very light cubical blocks. They are all practically insoluble in water.

The citrate is official only in the form of the solution. This is prepared by putting into a strong bottle a syrupy solution of magnesium citrate containing an excess of citric acid, adding potassium bicarbonate, and corking tightly. On account of its agreeable taste and effervescence, this preparation is much used as a purgative.

Magnesium sulphate, or Epsom salt, occurs in small, acicular, slowly efflorescent crystals, containing about 51 per cent. of water of crystallization, and soluble in their own weight of water at ordinary temperature. The taste is bitter, saline and nauseous.

Official Preparations:

Magnesii Carbonas .....½ to 1 drachm (2–4 Gm.).
Magnesii Oxidum .....½ to 1 drachm (2–4 Gm.).
Magnesii Oxidum Ponderosum.....½ to 1 drachm (2–4 Gm.).
Magnesii Sulphas .....2 to 8 drachms (4–15 Gm.).
Magnesii Sulphas Effervescens (50 per cent.).½ to 1 ounce (8–15 Gm.).
Liquor Magnesii Citratis.....6 to 12 fluidounces (180–360 mils).

Physiological Action.—Injected intravenously the magnesium salts are violent poisons, affecting primarily the medullary centers. The respiratory center no longer responds to asphyxia; there is also a fall of the blood-pressure due to a diminished activity of the vasomotor center, although this latter is generally not completely paralyzed. According to MacNider and Matthews, the heart muscle is so affected that it no longer originates contractions—or, if the dose is small, the contractions are greatly below the normal in their force—but is still capable of responding either to direct stimulation of the heart muscle or of the accelerator nerves. Meltzer and Auer have shown that when locally applied to the nerve-trunk, whether afferent or efferent, the solution of magnesium sulphate, or chloride of sufficient concentration, completely prevents the passage of impulses along them. With concentrated solutions, this paralytic action on the conductivity of nerve-trunks was rapid and complete, but even with solutions of 1.5 per cent. there was a distinct reduction in the functional activity of the nerve.

Although these effects from magnesium sulphate are not likely to occur from its oral administration because of the comparative non-absorbability of the salts of this metal, Boos has reported ten cases of poisoning, of which six ended fatally, which he attributes to magnesium. In several of these cases the element was recognized chem-

ically in the urine. The symptoms described, however, are so different as to suggest that in most of the cases they were due to some other cause.

Therapeutics.—As a cathartic, magnesium sulphate is probably the most efficient of all the group of salines, and, although somewhat disagreeable to take, may be used wherever this class of remedies is indicated. It is useful whenever it is desired to rapidly evacuate the upper bowel, as in enteritis, poisonings or acute constipation; its value in these conditions depends not only on its promptness but also on its comparative freedom from irritant effects. Because of the copious secretion of intestinal fluids it is also widely employed to assist in elimination, either of excessive water or of various toxic matters, from the system. Thus it is a favorite remedy in the treatment of dropsy and is generally believed to be useful in gout, uræmia, and other accumulations of toxic metabolites.

More recently magnesium sulphate has been employed for its paralyzing effect on nerve tissue. For this effect it has been injected into the spinal canal in the treatment of tetanus. It is probable that it is of service as a symptomatic remedy, but there is no reason to believe that it possesses any direct curative property or is greatly superior to other anti-convulsant measures. Three to four drachms (8 to 12 mils) of a 15 per cent. solution may be injected into the subarachnoid space, of course employing due aseptic precautions. It has been similarly employed to a limited extent in the production of the so-called spinal anæsthesia. Concentrated solutions of magnesium sulphate have been widely used as local applications in various inflammations, such as sprains, erysipelas, and the like, with asserted beneficial results.

The oxide and carbonate are antacid as well as laxative. For their purgative powers they are probably dependent upon the presence of acids in the primæ viæ, and hence their effects vary. When taken repeatedly they are said at times to accumulate in the intestines, and should not be used as an habitual laxative. They are often given along with Epsom salt or senna, on account of their antacid properties. Their chief use is in acute acid dyspepsia, in sick headache, in diarrhœa with excessive acidity in children, in gout, in rheumatism, and in various cutaneous affections—wherever, in a word, a laxative antacid is indicated. It may be noted that magnesium oxide will neutralize four times as much acid as will the same quantity of sodium bicarbonate. An excellent antacid preparation is the newly official suspension of magnesium hydroxide, *Magma Magnesiæ*, popularly called "milk of magnesia"; one teaspoonful of this is equivalent to 3 grains of magnesium oxide.

PHENOLPHTHALEIN.

The dihydroxy-phthalophenone has long been used in chemistry as an indicator for alkalies. In 1900 it was accidentally discovered that this substance possessed laxative properties. Phenolphthalein occurs

as a white or slightly yellowish crystalline powder, odorless and with a very faint taste. It is practically insoluble in water but fairly soluble in alcohol. In aqueous solutions of the alkalies it is dissolved with the production of a red color.

Although when injected into the blood stream phenolphthalein is slightly irritant to the kidneys, it has almost no toxic effects; I have administered intravenously to dogs doses equivalent to 60 grains for a man with no perceptible alterations in the circulation or respiration. The laxative action appears to be due to a mild irritation of the intestinal mucosa, causing an increase of secretion and probably also of peristalsis. The action is chiefly upon the small bowel.

Phenolphthalein is a valuable laxative in the treatment of mild constipation, whether acute or chronic. The movements are soft and usually unaccompanied with griping, and occur within four to eight hours. One great advantage of the drug is its ease of administration; because of its tastelessness it is often exhibited to children in the form of candy. For adults it is best administered in tablets. Some clinicians have feared the possibility of irritation of the kidneys from its prolonged use, but the quantity absorbed from the intestinal canal is so small that this fear would seem unfounded, and I have administered it daily for many weeks without any perceptible evil effect. Sometimes when used continuously the alimentary canal appears to become accustomed to its action, and it is therefore well to vary with some other cathartic. The ordinary dose is one to two grains.

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CHAPTER VI.

DRUGS AFFECTING METABOLIC PROCESSES.

In this chapter are included a number of substances our belief in whose efficacy and our idea of whose mode of action depend more on prolonged clinical experience than upon any scientific studies of their effects on the system. Pharmacologists are, however, not solely blamable for our ignorance of the mode of action of these drugs, because most of them find their value in conditions of whose pathology we are almost entirely ignorant, and it is hardly to be expected that pharmacologic science should explain in what way a drug corrects a morbid process when the pathologist is ignorant of what that morbid process is. It is of considerable interest, in this connection, to note that within the last few years the recent advances in our knowledge concerning the causes of those diseases which the older writers included under the generic term dyscrasias have enabled us to explain what were formerly the mysterious effects of the so-called alteratives. For example, many years ago the effects of quinine in malaria were attributed to some nebulous antiperiodic influence until the discovery of the etiology in the plasmodium permitted the demonstration that the action of this drug was due to its poisonous effect on lower forms of animal life. In the same way the discovery of the causative relation of the Spirochæta pallida to syphilis has explained the beneficial action of mercury in this connection. It is probable, however, that the good results which have followed the so-called alteratives in many instances have been brought about through a modification of the chemical changes in the bodily cells.

In passing, the author would like to register a protest against that widely-used but meaningless term "General tonic" which too often serves as a cloak for the physician to hide his ignorance of the underlying pathology of his patient's symptoms. There can be, from the stand-point of the scientific therapeutist, no such thing as a general tonic. A drug may, by stimulating the circulation or by improving the quality of blood, bring more or better nutrition to starved cells and thus increase the general strength of the patient, but because digitalis or strychnine improves the bodily condition through its influence upon the circulation does not remove them from the class of circulatory stimulants. Again, a drug like arsenic, by its effects upon the oxidative processes, may lead to an increase in weight, but we should employ it not for any mysterious "tonic" influence, but for its influence in lessening destructive metabolism.

IRON.

Materia Medica.—The preparations of iron recognized by the United States Pharmacopœia are ridiculously redundant. The solid salts may be conveniently divided into two groups—the soluble and

the insoluble. The soluble salts of iron may be further subdivided into those in which the base is combined with an inorganic acid and those containing an organic acid radical. These latter salts are probably not chemical individuals but mixtures of salts of iron with various other salts. They occur in commerce in the form of thin translucent pieces, whence they are collectively known as "scale" salts. A large number of these scale salts have been prepared, but the Pharmacopœia at present recognizes only three, the *iron and ammonium citrate,* the *iron and quinine citrate,* and the *iron phosphate.* In the first two the iron salt is made soluble by the presence of ammonium citrate, and in the last by sodium citrate. The iron and ammonium citrate occurs in iridescent garnet-red scales, somewhat deliquescent, the iron and quinine citrate is of a greenish-yellow color, and the iron phosphate a bright green. All of them are freely soluble in water and insoluble in alcohol.

Of the inorganic salts of iron which are recognized by the Pharmacopœia, the most important are the sulphate and the chloride. *Ferrous sulphate,* or copperas, occurs as pale bluish-green prisms with a saline styptic taste, which rapidly lose their water of crystallization in dry air; in moist air oxidation takes place and the crystals become covered with the brownish basic ferric sulphate. The dried ferrous sulphate is prepared by driving off the water of crystallization with the aid of heat; it is a grayish-white powder. Both of these forms of the sulphate of iron are freely soluble in water.

Ferric chloride occurs in orange-colored pieces freely soluble in either water or alcohol. It represents about 20 per cent. of metallic iron and is extremely deliquescent. The solution of iron chloride, which is made directly by acting upon iron wire with hydrochloric acid, is a brownish liquid, highly acid, and represents about 10 per cent. of metallic iron. Tincture of the chloride contains 35 per cent. of this solution diluted with alcohol.

Besides these salts, the Pharmacopœia also recognizes metallic iron, both in the form of iron wire and in the form of the powder. Powdered iron is obtained by reducing subcarbonate of iron by heating in the presence of hydrogen. It is officially known as reduced iron, but is also popularly called Quevenne's iron. It is a very fine grayish powder which undergoes rapid oxidation on exposure to the air.

When an alkali is added to a solution of a ferric salt there is formed a brownish precipitate of *ferric hydroxide*—$Fe(OH)_3$—which is a useful chemical antidote to arsenic. On standing the ferric hydroxide absorbs oxygen and forms more basic hydroxides which are much less efficient precipitants of arsenic; it is essential therefore that this antidote always be freshly prepared. The Pharmacopœia recognizes a mixture made by adding magnesium oxide to a solution of ferric sulphate.

A word may be said in this place concerning the so-called "organic iron." As is well known, a number of the tissues of the body contain

considerable amounts of iron in combination with various protein bodies. These ferruginous compounds differ from the ordinary salts of iron in failing to give certain characteristic chemical reactions—such as the black precipitate with the ammonium sulphide and the formation of prussian blue with ferrocyanides. Because of this failure to respond to the ordinary tests for iron, these compounds are sometimes spoken of as "masked" iron, but more frequently the term organic is applied to them, although this is unfortunate, because of the liability to confusion with the combinations of iron with organic acids which do not appear to differ in their chemical properties from the inorganic salts of iron. An immense number of preparations of iron belonging to this class have been devised by chemists. It should be noted, however, that many of the proprietary preparations which are put upon the market as organic iron do not correspond in their chemical properties to the claims made by their manufacturers. Concerning the relative value of the masked forms of iron and the inorganic salts in therapeutics more will be said anon.

Official Preparations (the important ones are marked †):

The soluble solid preparations of iron are as follows:

Ferri Chloridum (22 per cent.*).....1 grain (0.06 Gm.).
† Ferri Phosphas (12 per cent.).....5 grains (0.3 Gm.).
Ferri Sulphas (20 per cent.).....2 grains (0.13 Gm.).
Ferri Sulphas Exsiccatus .....1 grain (0.06 Gm.).
Ferri Sulphas Granulatus.....2 grains (0.13 Gm.)
† Ferri et Ammonii Citras (16 per cent.).....5 grains (0.3 Gm.).
Ferri et Quininæ Citras (13 per cent.).....5 grains (0.3 Gm.).

The insoluble preparations are:

Ferrum (Iron Wire).....Not used internally.
† Ferrum Reductum (90 per cent.).....1 to 3 grains (0.06–0.13 Gm.).
Ferri Carbonas Saccharatus.....3 to 5 grains (0.2–0.3 Gm.).
† Massa Ferri Carbonatis [Vallet's Mass] (20 per cent.) .....3 to 5 grains (0.2–0.3 Gm.).
† Pilulæ Ferri Carbonas [Blaud's pills].....1 to 3 pills.
Ferri Hypophosphis (22 per cent.).....3 grains (0.2 Gm.).
† Ferri Hydroxidum cum Magnesii Oxido....½ to 4 fluidounces (15–120 mils).
Pilulæ Ferri Iodidi.....2 pills.

The liquid preparations containing iron are:

Liquor Ferri Chloridi (10 per cent.).....3 to 5 minims (0.2–0.3 mil).
† Tinctura Ferri Chloridi (4.8 per cent.).....10 to 30 minims (0.6–2.0 mils).
† Liquor Ferri Subsulphatis (13.6 per cent.).3 to 5 minims (0.2–0.3 mil).
Liquor Ferri Tersulphatis.....To make the Hydroxide.
† Liquor Ferri et Ammonii Acetatis [Basham's Mixture].....4 fluidrachms (15 mils).
† Syrupus Ferri Iodidi.....15 to 30 minims (1–2 mils).

* The percentages given refer to the proportion of *metallic* iron present.

Physiological Action.—*Absorption.*—A number of years ago Quevenne showed that the amount of iron in the urine was not noticeably increased after the oral administration of the ordinary salts of the metal. This fact, which was subsequently confirmed by Bunge and many other chemists of recognized standing, led to the teaching that the inorganic salts of iron were not absorbable from the alimentary canal. This fact led to the promulgation of an extraordinary theory concerning the mode of action of iron in chlorosis, which, although originally suggested by Kletzinski, is commonly known as Bunge's theory. According to this theory, iron was useful in chlorosis because this disease was due to excessive formation in the intestinal tract of hydrogen sulphide, which precipitated the iron ordinarily taken with the foodstuffs as an insoluble sulphide, preventing its absorption, and the inorganic salts of iron did good by combining with the sulphides and thus protecting the food iron from precipitation.

The objections to the theory are: first, that not all cases of chlorosis show an excessive production of hydrogen sulphide; secondly, that hydrogen sulphide does not form insoluble sulphides with food iron; thirdly, that the presence of hydrogen sulphide in the intestinal tract in large amounts does not produce anæmia; and, finally, that other metals which combine with hydrogen sulphide are valueless in this condition.

Although the quantity of iron in the urine is only very slightly increased after the administration of salts of the metal by mouth, the deduction that the iron is, therefore, not absorbed is unjustified and erroneous. In the first place, it must be remembered that the kidneys are not the only channels of excretion. A number of substances are eliminated more largely through the glands of the intestinal tract than they are through the kidney, and Gottlieb has recovered, after the hypodermic administration of a salt of iron, 97 per cent. of the quantity administered from the feces, showing that iron is among those substances which escape from the system largely through the intestines. Moreover; there is abundant evidence of a direct nature that iron is absorbed from the intestinal tract. Kunkel for eight weeks fed two dogs upon milk, giving to one of them iron in addition, and bleeding each dog equally from time to time. After the killing of the dogs the blood and the various organs of the body were carefully analyzed, and it was found that iron was in distinct excess in all the organs of the dog to which the metal had been given, and that in the blood there was one and a half times as much of the iron, and in the liver eight times as much, as in the similar tissues or organs of the dog used for control.

Taking advantage of the fact that the iron combined in the protoplasmic molecules did not react to ammonium sulphide, Justus Gaule detected, chemically, iron in the lymph coming from the thoracic duct of a rabbit into whose stomach a dilute solution of the ferric chloride had

been injected. Quincke not only proved that iron is excreted from the mucous membrane of the large intestine, but also that absorbed iron can be detected in the walls of the duodenum, a fact which has been confirmed by Hall, by A. Hoffmann, and by Hare. Hall further discovered that if the feeding of a carnivorous animal with iron had been long continued, the metal could be detected in the pulp-cells of the spleen and in the hepatic acini around the central vein. The conclusion of Hall, that iron occurs in the human system in two forms, one a fixed organic combination—hæmoglobin—the other an inorganic or a very loose organic combination, is very plausible. According to Hall, it is the second combination whose amount in the system continually varies with that of the iron taken into the alimentary canal.

There is, therefore, no longer room for doubt but that iron administered by the mouth is freely absorbed from the intestinal tract, nor is there any reason to believe that the masked iron is absorbed any more readily than the official preparations. Concerning the form in which the iron is absorbed we have, however, no knowledge.

Action on Blood-making Organs.—It has generally been held that the value of iron in chlorosis and other forms of anæmia depended upon the fact that it offered to the system the essential constituents of the hæmoglobin which were lacking; in other words, that its action was practically that of a food.

To suppose that, because it is an essential constituent of hæmoglobin, iron acts in the treatment of anæmia as a food, is no more relevant than to claim that, because phosphorus is an essential constituent of the protoplasm, therefore the administration of elementary phosphorus acts as a food; or to claim that, because strychnine is not a normal constituent of the protoplasm, therefore it exercises no beneficial action upon the system.

The theory of the food action of iron is rendered, it seems to the author, quite untenable by the following facts: First, the amount of iron which is needed for the daily consumption is extraordinarily small, not surpassing more than 10 milligrammes (grain ⅙) per day, whereas the amount required to produce therapeutic results is often forty or fifty times this quantity; second, many cases of chlorosis are not in the least benefited by increasing the quantity of iron-containing foods—in other words, that the ordinary food iron which is the common source for the iron in the body-cells is not capable of benefiting cases of true chlorosis; and, third, the iron has been traced still in the inorganic state as far as the spleen. The author, therefore —while not denying the possibility of occasional cases of iron starvation in which the salts of this metal may be utilized as a food—believes that in the true chlorosis iron acts as a direct stimulant to the blood-making organs in the same way that strychnine stimulates the nerve-centers in the spinal cord or caffeine excites the kidney to higher functional activity.

The conclusion that iron acts as a drug rather than a food is

rendered further probable by the observations that in cases of chlorosis not only is the quantity of hæmoglobin increased by iron, but that there is also augmentation in the number of blood-globules, and that in dogs rendered anæmic through repeated bleedings the administration of iron increases the nucleated corpuscles in the blood.

Therapeutic Uses.—There is, perhaps, no drug in the pharmacopœia, with the possible exception of strychnine, which is more frequently employed in cases in which it cannot prove of any possible benefit than iron. Although clinicians speak of iron as a "general tonic," there is not sufficient evidence that it has any influence upon the body, aside from its effect upon the blood-making organs, which could be of any service in the treatment of disease. The use of iron should be limited, aside from the local employment of certain salts of it, to conditions in which there is anæmia.

The anæmias may be divided into three classes: (1) The accidental anæmias, such as are seen after severe hemorrhage, certain wasting diseases, etc. (2) Anæmias belonging to the type of chlorosis. (3) Those belonging to the type of the so-called pernicious anæmia.

These anæmias can be differentiated symptomatically with a fair degree of accuracy by the relation of the number of corpuscles to the percentage of hæmoglobin. In the first type, the accidental anæmias, we find that there is an equal reduction in the number of corpuscles and in the amount of hæmoglobin; in chlorosis the reduction in the percentage of hæmoglobin is more than the diminution in the number of blood-cells, while in the pernicious anæmia the number of blood-cells is decreased proportionately. The distinction may be expressed in terms of hæmoglobin in each corpuscle: in the first type each corpuscle contains the normal quantity of hæmoglobin, in chlorosis each corpuscle contains too small an amount of hæmoglobin, while in the third type each corpuscle contains an abnormally large amount of hæmoglobin, although there is such a great reduction in the number of corpuscles that the total quantity of hæmoglobin is below the norm.

It is especially in the second type of anæmias that iron is of greatest service. The rapidity with which the blood improves in chlorosis under the influence of iron is often astonishing. Occasionally, however, cases of chlorosis are met which are rebellious to the drug; especially is this likely to be in the cases of relapse. The mistake is often made, in treating chlorosis, to allow the patient to drift from under supervision or to return to the previous circumstances and surroundings as soon as subjective symptoms have been relieved. If the treatment is cut short in this manner the patient is likely to retrogress until the blood picture may be as severe as, or even worse than, before any treatment. Such cases are frequently the most obstinate of all chlorotics. The treatment of chlorosis should never be considered finished until the number of corpuscles and the percentage of hæmoglobin are entirely normal.

In the secondary or accidental anæmias, iron is of some service

in those cases where the cause can be controlled; for instance, after an acute hemorrhage, iron will increase the rapidity with which the blood regains its normal condition. On the other hand, in those cases in which there is a constant destruction of blood-cells which cannot be prevented, as in cancers and cachexias, the iron is unable to maintain the quality of the blood in the face of the constant drain.

Various salts of iron have been attributed with possessing some mysterious specific properties in various diseases. Thus, the solution of iron and ammonium acetate—Basham's mixture—is almost as routinely ordered when a diagnosis of chronic nephritis is made, just as digitalis is in cases of heart-disease. In many cases of nephritis iron is of much service, but this is simply because these patients show marked anæmia, and iron is beneficial merely by improving the quality of the blood. Neither Basham's mixture nor any other preparation of iron has any specific action upon the kidney. With still greater positiveness the older clinicians insist on the specific action of tincture of chloride of iron in erysipelas and diphtheria. It is probable, however, that its beneficial effects in this condition are simply due to the hæmatinic action of the iron.

Some of the salts of iron are very powerfully astringent and used locally for the purpose of contracting tissue, but especially as styptics. The most important preparations of this class are the solution of ferric chloride and the solution of the subsulphate of iron commonly known as Monsel's solution. The latter is one of the most reliable agents for the control of gastric hemorrhage in doses of one to five minims, well diluted, repeated as often as necessary.

The ferric hydroxide, sometimes known as the sesquioxide of iron, is of value chiefly as an antidote to arsenic. It is formed when an alkali is added to a solution of any ferric salt. In emergency any alkali, even ammonia water, and any soluble ferric salt may be employed to make the antidote, but the official ferri hydroxidum cum magnesii oxido, which is made by adding an excess of magnesium oxide to a solution of ferric sulphate, has the advantages that the magnesia is non-irritant and is itself somewhat antidotal to arsenic.

Administration.—When iron is used for its chalybeate effect a preparation should be chosen which is as free from astringency as possible. There is no necessity of, nor advantage gained from, irritating the stomach or locking up the intestinal secretions in a case of chlorosis. Most of the unions of iron formed with the inorganic acids, such as the chloride and the sulphates, are powerfully astringent and, therefore, unsuited for use as hæmatinics. Metallic iron, which is recognized under the name of ferrum reductum, is entirely free from astringency and probably equal in its chalybeate properties to any salt of iron, and has the advantage, when given in pill form, that because it represents 90 per cent. of metallic iron its dose is smaller than that of any form of iron intended for internal administration.

The pill of ferrous carbonate is likewise a valuable form of iron and widely employed under the name of Blaud's pill. Each pill weighs about five grains and represents approximately one-half grain of iron. If it is desirable to administer the iron in solution, either the soluble phosphate or the iron and ammonium citrate or the iron and potassium tartrate may be employed. In administering iron in solution it is well to remember that it is incompatible with nearly all vegetable tinctures because of the tannic acid in the latter. The official combinations of iron with the powerful alkaloids, such as the iron and quinine citrate, and especially the so-called triple elixir of iron, quinine, and strychnine phosphate, so widely employed by careless physicians, are entirely ineligible preparations which should never be prescribed, much less recognized, by a work of the dignity of the United States Pharmacopœia.

Solutions of iron are liable to discolor the teeth, due to the deposit of a sulphide. This can be easily removed by the dentist, and if care has been taken to avoid the highly acid salts, such as the chlorides, there is no permanent injurious effect.

Certain of the salts of iron, notably the chloride and the subsulphate, are sufficiently irritant that when taken in overdose they can give rise to violent, and even fatal, gastro-enteritis. The best antidote is an alkali, as baking soda or soap. Tannic acid is also of service as an antidote.

PHOSPHORUS.

Materia Medica.—Phosphorus is a translucent, when pure nearly colorless, but usually slightly yellowish, highly inflammable elementary body, which is tasteless, but possessed of a peculiar alliaceous odor. It is insoluble in water, sparingly soluble in ether, absolute alcohol, and the oils, freely so in chloroform. It takes fire at 100° F., and melts at 111.2° F. In the shops it is in cylindrical sticks, covered with a whitish layer, and having, when cut, a waxy consistence and lustre.

There are several allotropic modifications of phosphorus known to chemists, but none of them have ever been shown to be possessed of any useful therapeutic virtues.

Official Preparations:

Phosphorus	$^1/_{100}$ grain (0.6 Milligm.).
Pilulæ Phosphori	Each $^1/_{100}$ grain (0.6 Milligm.). 1 pill.

Physiological Action.—*Absorption.*—Phosphorus, although insoluble in water, is taken up through the intestinal tract, probably in fatty solution, and enters the blood as elemental phosphorus and not in the form of phosphoric acid. It appears, however, after its absorption to be oxidized and excreted chiefly as phosphoric acid, although after toxic doses some of it may escape unchanged.

When administered in small doses over considerable periods of time phosphorus has a distinct influence upon the metabolism, apparently affecting chiefly the bones and nervous system and probably the blood-making organs.

So far as the nervous system is concerned, this assertion rests upon clinical observation; but Wegner (confirmed by S. Miura and W. Stoeltzner) has experimentally demonstrated such an action upon the bony tissues. When adult animals are fed upon minute doses of phosphorus the spongy tissue in the long and short bones becomes thickened and the compact tissue more dense. After a time new tissue is deposited upon the inside of the shafts of the long bones, in some instances until the marrow cavity is obliterated. The action upon the bones of growing animals is even more marked.

Phosphorus apparently stimulates also the blood-making organs, thereby causing an increase in the number of erythrocytes. It appears to differ from iron in this regard, in that it acts in normal as well as anæmic conditions.

Therapeutics.—Phosphorus is used in medicine for its influence on the developments of bone in osteomalacia, rickets, and other diseases of the bones. It is also used for the purpose of upbuilding the nervous system in cases of nervous exhaustion, and has even been employed, although with doubtful benefit, in conditions of actual degenerations of the nerve-centers, as in brain softening.

Toxicology.—The amount of phosphorus which is capable of taking life is extraordinarily small, as little as one-eighth of a grain having proved fatal. The chewing of the heads of two matches by an infant led to death from phosphorus poisoning. The symptoms generally do not appear for some time. Three to twelve hours after there develops a sense of weakness and general malaise with nausea and vomiting and more or less abdominal pain; the matters vomited often smell strongly of phosphorus and may be luminous in the dark; there is generally fever, loss of appetite, and thirst; the stools may be normal, or there may be either diarrhœa or constipation. Usually, after two or three days, there is a temporary remission of symptoms, the characteristic manifestations sometimes not developing for as long as six or seven days after ingestion of the poisoning. In the later stages there is vomiting, often bloody, severe jaundice, the liver is enlarged and painful, the urine is scanty, albuminous, contains bile-pigments, also, occasionally, leucin and tyrosin. The appearance of sarcolactic acid in the urine has been held to be characteristic of phosphorus poisoning. There is usually, in the later stages, severe nervous symptoms, consisting of delirium, somnolence ending in coma, occasionally preceded by convulsions; sometimes spasms and fibrillary contractions of the muscles occur, although in prolonged cases there is generally paresis of the voluntary muscles.

After death wide-spread pathological changes are found in the body. The most characteristic of these are fatty degenerations in-

volving practically all the organs—but especially marked in the gastro-intestinal mucosa, in the liver, and in the kidney—inflammation of the glands around the pylorus, and hemorrhagic extravasations into the subcutaneous and submucous tissues.

Treatment.—The indications for treatment in phosphorus poisoning are very evident. It is plain that no medication can influence the terrible organic lesions induced, and that the primary object must be to prevent the absorption of the poison. Emetics and purgatives are, therefore, of prime importance. The necessity of the persistent use of evacuants is shown by the finding of phosphorus by Starck in the stools three and a half days, and in the vomit two days, after the ingestion of the fatal dose. As phosphorus is soluble in oils, *no fatty matters* should be allowed either in the food or in the medicines. The most valuable antidotes are copper sulphate and potassium permanganate. As an emetic, *copper sulphate should always be chosen.*

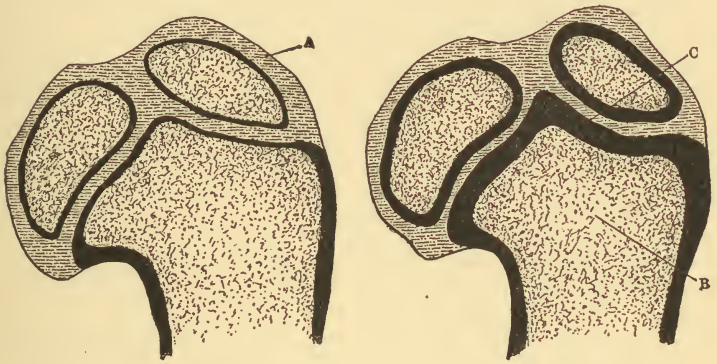


FIG. 26.—The effect of phosphorus on the growth of bone. *A*, cartilage; *B*, cancellous tissue; *C*, thick deposit of dense bony substance at point of growth of the bone.

Chronic Poisoning.—Match-makers and other artisans who are exposed by their occupations to the fumes of phosphorus suffer from chronic poisoning, which is especially distinguished by the occurrence of necrosis of the upper or lower jaw. It occurs chiefly in those artisans who have bad teeth, and the experiments of Wegner have demonstrated that the necrosis of the jaw is due to the local action of the vapor of phosphorus.

ARSENIC.

Materia Medica.—Metallic arsenic is not employed in medicine. The substance ordinarily referred to as arsenic in medical parlance is the arsenous anhydride, known officially as arsenic trioxide. This substance, which is sometimes incorrectly called arsenous acid, is

obtained as a by-product in smelting certain European ores, notably the cobalt ores of Germany and the iron ores of England. It occurs either in transparent glass-like pieces or in the form of a white crystalline powder. It is soluble in water, the crystalline variety being the least so. Boiling water will dissolve one-fifteenth of its weight of either variety. It is odorless and almost tasteless, but when heated it emits a garlicky odor, owing to its first being reduced to a metallic state and then volatilized.

Besides the anhydride, the United States Pharmacopœia recognizes the iodide of arsenic and also sodium arsenate, and a solution of potassium arsenite. *Arsenic iodide* is an orange-red crystalline powder soluble in twelve parts of water, which is decomposed by light. It is comparatively rarely employed. *Sodium arsenate,* Na_2HAsO_4, when dry, is an amorphous white powder freely soluble in water, odorless and with a faintly alkaline taste. It takes up seven molecules of water and forms colorless transparent crystals.

Official Preparations:

Arseni Trioxidum	1/60 to 1/30 grain	(1–3 Milligm.).
Arseni Iodidum	1/30 to 1/10 grain	(3–6 Milligm.).
Sodii Arsenas	1/12 to 1/6 grain	(5–10 Milligm.).
Sodii Arsenas Exsiccatus	1/30 to 1/10 grain	(3–6 Milligm.).
Liquor Acidi Arsenosi (1 per cent.)	5 to 10 minims	(0.3–0.6 mil).
Liquor Sodii Arsenatis (1 per cent.)	5 to 10 minims	(0.3–0.6 mil).
Liquor Potassii Arsenitis [Fowler's Solution] (1 per cent.)	5 to 10 minims	(0.3–0.6 mil).
Liquor Arseni et Hydrargyri Iodidi [Donovan's Solution] (1 per cent. each of Arsenic and Mercuric Iodides)	3 to 5 minims	(0.2–0.3 mil).

Physiological Action.—Arsenic is a protoplasmic poison capable of destroying all forms of life. Because of its high toxicity to man it is rarely useful as a bactericide, but it appears to have a selective toxicity for protozoa, and it is probable that many of its uses in clinical medicine depend upon this power.

General Action.—Although the large dose of arsenic has a powerful influence upon the nervous system and circulation, there is apparently no connection between this action and its therapeutic usefulness. In toxic doses in the frog it produces, first, a paralysis of voluntary motion, followed by a loss of reflex action, and would seem, therefore, to act as a paralyzant of the central nervous system, affecting the cerebral motor area before the spinal. The large dose is also a circulatory depressant, lowering blood-pressure through vasomotor paralysis, and in still larger quantities acting as a depressant to the heart muscle also.

Blood.—Arsenic has a marked effect, although one not clearly understood, upon the blood-making organs. Small doses cause hyperæmia of the bone-marrow and an increase in the formation of

leucoblastic cells, with consequent increase of white blood-corpuscles, but without apparent change in the number of red cells. If the dose be a toxic one, this is followed by a hyaline degeneration of the bone-marrow, with decrease in both the number of white and red cells. The mode of its action in various anæmias is entirely inexplicable.

Metabolism.—Although the influence of small doses of arsenic on the chemical movements of protoplasm is not clearly understood in its details, it appears fairly well established that small doses diminish the catabolic processes of protein tissues. Either because of this action or through some other effect arsenic tends to increase the bodily weight, especially in young animals. Gies administered to half a litter of new-born rabbits small doses of arsenic and found, after a period of four weeks, that these animals averaged thirty per cent. heavier than the other half, and that the bones were longer and thicker and had undergone changes similar to those which have been described for phosphorus.

The effect of arsenic upon nutrition is especially evident in the changes in the skin. After large doses there is a marked stimulation in the growth of the epithelium, especially in the modified dermal tissues such as the finger-nails, with a tendency for deposit of pigment.

Arsenic Eating.—In the duchy of Styria in Austria, and probably also in other portions of the world, a considerable portion of the population are in the habit of using arsenic habitually in large doses. These peasants become gradually accustomed to the drug until enormous quantities are taken, even up to six or seven grains at a dose. Although Cloetta has shown that tolerance in dogs is due to impeded absorption, there appears to be formed in these persons a true tolerance for the drug, since large quantities have been recovered from the excretions. These peasants assert that the effect of the metal is beneficial to health, improving the complexion and muscular endurance.

Therapeutic Uses.—The uses of arsenic come under two heads—those which are due to its influence upon nutrition and those due to its influence upon pathogenic parasites.

Among the conditions for which its nutritive effects make it valuable are various skin diseases. It is of value especially in chronic conditions and where the disease is superficially seated. In acute inflammatory diseases of the skin it is to be avoided. It is most widely used in psoriasis and chronic eczemas, but is also serviceable in various other chronic dermal affections.

Arsenic appears to have some special relation with the thoracic organs, and is widely used in chronic bronchitis, especially when associated with asthma. Its value in phthisical conditions, however, depends probably rather on its influence on nutrition increasing the general bodily health rather than any specific effect upon the lungs. In consumptive patients who have ceased to gain weight with the

ordinary dietetic management the addition of arsenic will often stimulate the reconstructive processes to renewed activity.

Concerning the action of arsenic in diseases of the blood, while there is abundant clinical evidence that in many of them it is of great value, the mode of its action is not known. In some of them its effects are probably due to actions upon some parasite; in others, however, if it possesses any influence, it must be a direct one upon the blood-making organs. In chlorosis, although it has comparatively little beneficial action when given by itself, in some way it appears to enhance the usefulness of iron and is especially of service in those cases which have proven rebellious to simple chalybeate treatment. It is also of much value in pernicious anæmia. It is doubtful whether it ever leads to a complete recovery in this most hopeless condition, but in many cases it causes, at least temporarily, a marked improvement both in the blood and the general health of the patient. It is also of much service in leukæmia, Hodgkin's disease, and allied disorders.

In chorea arsenic has long enjoyed the reputation of being our most certain remedy, although of the mode of its action we have no knowledge whatsoever.

Antizymotic Uses.—Arsenic, especially when in organic combination with a methyl radical, has a powerful effect upon certain lower forms of life, notably upon pathogenic protozoa. It has for many years been known to be of great service in certain types of malarial infections. In the ordinary tertian or quartan fevers it is greatly inferior to quinine, but even here is of some value when this alkaloid for any reason is unavailable. In the chronic types of malarial fever which have been treated with quinine without complete recovery arsenic is of considerable service. It is used especially, however, in the convalescence from acute malarial fevers after the fever has been broken with quinine. While some authorities believe that its influence in this state is chiefly due to an effect upon the blood-making organs, it is highly probable that its service depends, at least in large part, upon a destruction of some parasites which may not have been killed by the cinchona alkaloid.

It is also of service in trypanosomiasis and in spirochætic inflammations, although in these latter conditions the organic derivatives of arsenic are much more potent than the inorganic salts.

As a caustic, arsenic is energetic and powerful, but somewhat slow, and causes intense pain, with violent inflammation of the neighboring parts. It is stated to affect more rapidly morbid than normal structures, and is especially used for the destruction of malignant growths. It appears to act chiefly upon the vitality of the part, acting, when sufficiently diluted, as a powerful irritant, and when in a concentrated form producing an irritation so intense that life cannot endure it. Hence, probably, the reason of its affecting more rapidly morbid growths, which have a lower vitality than sound tissues.

The great objection to the employment of arsenic is the possibility

of its absorption in sufficient amount to cause constitutional symptoms: even death has resulted from its external use. Since absorption takes place much more rapidly in a healthy than in an intensely inflamed or a dead tissue, whenever arsenic is employed as a caustic it should be used so freely as to kill the tissues rapidly, and under *no* circumstances should it be applied to a fresh wound. Used in any way, arsenic is a hazardous caustic, and it ought to be employed only with the knowledge and distinct remembrance of this fact.

It is, in the hands of the expert, a valuable agent for the destruction of malignant growths, especially epithelioma, for which purpose it should usually be diluted by mixing with starch or some similar inert substance. It may be applied in the strengths of from ten to twenty-five per cent., and generally allowed to remain on the part for eighteen or twenty-four hours, or sometimes longer, when the whole amount of diseased tissue comes away, often in one large slough, and complete healing is not uncommon.

Administration.—When arsenic is used merely for its effect on metabolism it is usually sufficient to give it in moderate doses—1/30 to 1/20 of a grain three times a day—continuously for such a period of time as may be necessary. In many cases, however, especially in chorea and leukæmic conditions, it is essential that the remedy be given to the limit of tolerance. Under these circumstances a liquid preparation should be chosen and given in moderately large doses, increasing the dose until the symptoms of the therapeutic limit have been reached. The solution of potassium arsenite is well fitted for this purpose, and one may begin with doses of five minims three times a day, increasing one minim each day until the limit of the patient's tolerance is reached. The symptoms which under these circumstances give warning that too much of the drug is being employed may be evidences of gastro-intestinal irritation, such as loss of appetite, nausea, abdominal distress, or diarrhœa, or, in many cases, the earliest sign is a puffiness about the eyes, generally most marked in the morning. When any of these symptoms are reached the dose should be immediately decreased.

Toxicology.—In acute arsenic poisoning the symptoms generally begin in from one-quarter to three-quarters of an hour with an intense burning pain in the œsophagus and stomach, soon spreading to the whole belly, and often accompanied by a sense of constriction at the throat and an acrid, metallic taste. In a very short time violent vomiting and purging come on. The vomitus may be bilious or even bloody; the stools are copious and watery. As the case progresses the thirst becomes excessive; the urine is suppressed; the extremities are icy cold; the pulse is small, feeble, and frequent; the rapid and labored respiration is very much embarrassed and painful from the abdominal tenderness; the surface is dark and cyanosed; violent cramps add their torture; exhaustion deepens into collapse; convulsions or coma ensues, and death occurs in from five to twenty hours.

If the dose has been somewhat smaller, these symptoms may be less violent and, after lasting for a few hours or a day or two, a remission will occur, purging and vomiting growing less, and even the abdominal tenderness disappearing in a great measure. But the persistent thirst, cold extremities, and albuminous urine show that the danger is not past, and after a time the case puts on a more alarming aspect. Fever develops, the tongue becomes dry and red, the belly very tumid, the abdominal pain more severe, dyspnœa and cyanosis occur, the face is swollen, nervous symptoms, tremblings, cramps, and convulsions appear, and finally an icy coldness pervades the frame, and death occurs in from two to six days. The mind is generally clear to the last. An eruption very frequently appears, sometimes as early as the second day, sometimes not until the fifth. Its character is various: thus, it may be petechial, urticaria-like, papular, vesicular, or pustular.

It should be remembered that atypical symptoms are not at all uncommon. In some cases the chief manifestation of its effect is profound collapse with or without coma.

When the poisoning is not fatal the convalescence is likely to be slow and interrupted by various disorders, especially of the alimentary canal and of the nervous system. After death from arsenic poisoning there are found very marked pathological lesions, the most obvious being those of severe gastro-enteritis, often with wide-spread degeneration of the protoplasm, the intestines may be covered with a false membrane and may closely simulate the pathological appearance seen in Asiatic cholera. Various changes in the nervous system, such as myelitis and neuritis, and granular degenerations of the spinal cord have been observed after acute, but much more common after chronic, arsenical poisoning. The ordinarily fatal dose is between two and three grains, although smaller quantities have killed and much larger have been recovered from.

Treatment.—If free emesis has not occurred before the patient is seen, a prompt emetic, as apomorphine or zinc sulphate, should be at once exhibited or the stomach washed out with the stomach pump. With the emetic, or sooner, if possible, the antidote should be administered. The most certain antidote is the *freshly precipitated ferric hydroxide,* which forms with arsenous acid a very insoluble compound. The antidote must be freshly prepared, and must be given in great excess; at least eight grains of the iron are required for the conversion of one grain of the arsenous acid, and the greater the excess the more prompt is the antidotal effect.

The best form of the iron antidote is probably the *Ferric Hydroxide with Magnesium Oxide* (United States Pharmacopœia). It is made by precipitating the solution of ferric sulphate by magnesia. But in practice any of the official ferric solutions—that of the chloride being generally preferred, as most readily procured—should be neutralized by sodium carbonate, or preferably by magnesia, and a portion of the

precipitate given at once, stirred up in *hot* water. The remainder of the antidote, having been hastily washed by emptying it on to a piece of muslin or in a filter, pouring water on it and allowing it to drain, should be administered very freely, indeed indefinitely, as it is entirely harmless.

In arsenical poisoning castor oil should be administered for the purpose of expelling the poison from the bowels, and demulcent drinks, opium, stimulants, dry external heat, and rubbing should be employed as called for by the symptoms. When there is a tendency to suppression of urine, very large draughts of feebly alkaline water should be given as frequently as the stomach will bear.

Chronic arsenical poisoning is often difficult of diagnosis; the symptoms are usually both local and constitutional. When the poison has entered the system through the respiratory tract the local irritation will be shown by dryness of the throat, coughing, and other evidences of chronic bronchitis or severe laryngo-bronchial catarrh. When the poison has entered the system through the alimentary tract, loss of appetite, with frequent vomiting and violent diarrhœa, is common. The general symptoms consist of depression of spirits, irritability, insomnia, giddiness, failure of memory, sometimes marked mental failure. According to Reynolds, in the English epidemic which was caused by arsenical beer, involvement of the nerve-trunks was very common. There were in these cases marked disturbances of sensation, paræsthesia, and partial anæsthesia, although complete anæsthesia was rare. There may be muscular tremors or stiffness; vertigo or other disorders of equilibrium are sometimes seen, while violent neuralgic pains, with numbness of the extremities, marked tenderness of the nerve-trunks, and other results of peripheral neuritis, are not rare. In most cases of chronic arsenical poisoning without a history the congeries of symptoms is, however, sufficient only to arouse suspicion and to call for a chemical examination of the urine. It should always be remembered that a peripheral neuritis is usually due to the presence of some poison, and that a group of wide-spread atypical symptoms not characteristic of any distinct disease is usually either toxic or diathetic.

Sometimes in acute, more frequently in chronic, arsenical poisoning, or as the result of long-continued medicinal use of the drug, certain disorders of the skin appear. Of these, herpes zoster seems to be the most frequent; it probably is the result of an arsenical neuritis. Another common skin affection is erythromelalgia, the painful red swelling of the epiderm. In protracted cases there is frequently thickening of the horny tissue in the palms of the hands and soles of the feet, which occasionally extends up the limb. The formation of transverse ridges across the nails, the result of the hyperkeratosis, has also been noted. The deposit of pigment in the skin and mucous membranes is an almost constant symptom—while there have been noted a number of other changes in the skin, such as

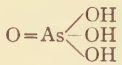
erythematous and desquamatous eruptions, urticaria and subcutaneous œdema, vesicular eruptions, bullæ, papules, pustules and ulcers, purpura, shedding of the hair and nails, and keratosis.

In those whose work brings them in contact with the poison, local toxic manifestations are not at all uncommon. These consist chiefly of low-grade inflammations of the dermal tissues, especially about the roots of the finger-nails. The only known treatment of chronic arsenical poisoning is to remove the patient from exposure and then treat symptomatically.

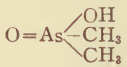
As arsenic figures perhaps more frequently than any other poison in criminal trials, it is well to remember that the finding of arsenic in the body is of itself no certain evidence of arsenical poisoning. Many of the embalming fluids used by undertakers contain large quantities of arsenic, and it has been shown that the poison even when injected after death may spread itself all over the body.

CACODYLIC ACID.

Under the name of cacodylic acid has been widely used in medicine, especially in the form of its neutral salts, the dimethyl-arsenic acid.



Arsenic acid.



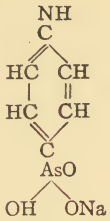
Cacodylic acid.

The U. S. Pharmacopœia recognizes the sodium cacodylate only. This is freely soluble in either water or alcohol, and is usually given in doses of from ¼ to 2 grains (0.02 to 0.12 Gm.).

As pointed out on page 20, poisonous elements or radicals may be so firmly bound up into complex molecules as to be non-ionizable, under which circumstances they will no longer exercise their ordinary toxic action. Such is the case with the arsenic in cacodylic acid; but the molecule undergoes in the body a slow demethylization with the liberation of the arsenic in an active state. This chemical change takes place in the human mechanism so slowly that a large amount of the arsenic is eliminated still in the non-ionizable form, and therefore quantities of arsenic sufficient to cause death if given in an inorganic combination cause no serious injury. Heffter has found that from 2 to 10 per cent. of the arsenic is liberated from cacodylic acid, the remainder of the compound being eliminated unchanged. Its therapeutic virtues probably depend upon the arsenic which is liberated in the system, and its range of usefulness is precisely the same as that of arsenous acid. It has, however, been chiefly employed in the treatment of various blood dyscrasias, such as chlorosis, pernicious anæmia, or leukæmia. Its advantage over the arsenous acid is that it can be administered hypodermically and can therefore be used with less danger of gastric disturbance. It is occasionally given by mouth, but is liable to cause an unpleasant garlicky taste. The iron cacodylate is also frequently employed, espe-

cially as a means of administering iron and arsenic hypodermically. The dose of it is about 1 grain.

Under various trade names, such as atoxyl and soamin, has been employed the sodium salt of paramido-phenyl-arsenic acid.



Atoxyl.

Atoxyl, which also contains arsenic in a non-ionizable form, is still more slowly decomposed in the body than the cacodylates. Certain pathogenic parasites, however, appear to decompose atoxyl more readily than the cells of the human body, consequently the drug is more poisonous to these micro-organisms than to their host. In this fact is found the explanation of the beneficial effects of a number of the organic compounds of arsenic in various infections. While atoxyl has been shown to be highly poisonous to the organisms which cause relapsing fever, frambesia, etc., because of its occasionally violent effects on the human being, its use at present is very largely limited to the treatment of trypanosomiasis.

Although usually the decomposition of the atoxyl molecule takes place slowly, under certain conditions at present not well understood, it may occur so rapidly as to produce the lesions of acute arsenic poisoning, especially peripheral neuritis. The most common of the more serious symptoms of this nature has been atrophy of the optic nerve with consequent permanent blindness, but other manifestations of arsenic poisoning, and even death, have resulted. For this reason atoxyl has been largely abandoned as a practical remedy. In the sleeping sickness of Africa, however, no drug has as yet been found which has given as good clinical results, and the condition is so desperate a one that despite the occasional cases of blindness seen from the treatment its employment is justifiable. According to the investigations of Koch, even in the advanced cases, it causes a temporary disappearance from the blood of the trypanosome, and in the earlier stages sometimes produces permanent cures. Koch recommends in this disease the hypodermic injection of 0.5 Gm. (8 grains) on two succeeding days, repeating the injections at ten-day intervals over a period of several months.

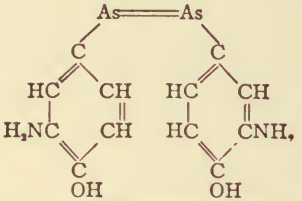
Atoxyl is also of great scientific interest because of the fact that it offered the starting point for the development of other arsenicals, notably salvarsan.

SALVARSAN.

Salvarsan is the proprietary name for the hydrochloride of dioxy-diamido-arseno-benzol. It is a yellow powder freely soluble in water and methyl alcohol, but less so in ethyl alcohol. It is an acid substance and forms with sodium two sets of compounds—a monobasic salt which is soluble in water and a dibasic salt which is insoluble in water, although soluble in an excess of alkali.

Under the name of *neo-salvarsan* the methanal sulphoxylate compound of salvarsan has been introduced. Its advantage lies in its greater solubility. It represents approximately two-thirds the quantity of arsenic.

The dose of salvarsan is generally stated as from five to nine grains (0.3 to 0.6 Gm.), and of neo-salvarsan as from seven to thirteen grains (0.4 to 0.9 Gm.), but Hagerty reports a death with symptoms of acute arsenic poisoning following two doses of 0.6 Gm. of neo-salvarsan given six weeks apart.



Para-diamido-dioxy-arseno-benzol.

In a considerable proportion of cases in which arsenic is used for the destruction of hæmatozoic parasites, although there may be a complete destruction of the micro-organisms from the blood, after a period of time there will be a recrudescence of the disease. This is due to the fact that a few of the infecting organisms have survived the attempt at their destruction and gradually multiply in the system until they reach sufficient numbers to cause clinical manifestation. Repeating the arsenical treatment under such conditions does not produce the same degree of benefit that the first administration did, and after a period of time the drug no longer produces any amelioration of the condition. It appears that under the prolonged exposure to small doses of arsenic the hæmatozoa develop a tolerance for the poison very much as do the higher animals. Ehrlich conceived the idea that if it were possible to find an arsenical preparation which was practically innocuous toward the human host but retained its toxicity to the infecting micro-organism, a sufficient quantity might be given at a single dose to destroy all the parasites in the system at once before they could develop a resistance toward the element. After a large amount of experimentation he finally found a preparation which was so highly poisonous toward the spirillæ group of germs—among which belong the causative agents of syphilis and of relapsing fever—and so slightly injurious to mammals that it gave prom-

ise of being able to accomplish this remarkable effect. This preparation was first distributed to certain prominent clinicians for practical tests under its laboratory number 606, and later put upon the market under the trade name of salvarsan.

Physiological Action.—Large single doses of salvarsan may produce acute poisoning. The symptoms produced under these circumstances are not the same as those of acute arsenical intoxication and are due to the action of the salvarsan molecule as a whole. When, however, repeated doses are administered, enough of the molecule may be decomposed in the system to produce arsenical poisoning.

Elimination.—Salvarsan appears to be eliminated with great slowness. It is partially broken up in the body, considerable quantities of arsenic trioxide having been found in the kidneys and in the liver. After intravenous injections the elimination begins in one-half hour and is completed in from four days to two weeks, and after intramuscular injections it is complete in generally two weeks, but arsenic has been detected in the urine as long as six months after its administration.

Therapeutic Value.—Although the early results obtained with this drug were so brilliant that many were led to believe that an immediate cure for syphilis had been discovered, time has shown that they were over-enthusiastic. While there is no room for doubt that salvarsan is an extremely valuable addition to our armamentarium against this dread disease, it is well established that only in a small percentage of cases will it destroy at once all the spirochetes, thereby producing a permanent cure. Because the relapses which have followed its employment must have been due to a certain number of organisms escaping the action of the drug for one reason or another, recourse was had to repeated injections with the idea that it might finally be possible to reach all of the germs, but this very effort is a confession of the failure of the drug to realize its purpose, and while repeated injections do produce better results than single doses, it is doubtful whether with any method of administration a larger percentage of complete cures can be accomplished with salvarsan than with mercury.

The most marked effects from this drug are seen in the beginning of the disease; the earlier the salvarsan is administered the greater will be the benefit from its use. The especial value of the drug lies in the fact that it will cause an almost immediate disappearance of the superficial lesions—such as the mucous patch—and thus lower the infectivity of the patient. Aside from this advantage the drug is also useful as an addition to our older methods of treatment, for the great mass of syphilographers seem to be convinced that by following a course of salvarsan injections with prolonged mercurial treatment better results are obtained than are possible with either remedy alone.

The remedy has further failed of complete realization of Ehrlich's hopes in that it is not completely innocuous to the human host. There have been reported several deaths which seem directly attributable to

its use. These deaths, it should be remarked, are relatively infrequent, the mortality certainly being not over one in 3,000 administrations, and Ehrlich himself asserts that if properly used it is not over one in 30,000. Among other evil effects which have been attributed to the remedy have been reported neuritis of the optic and auditory nerves, leading to permanent loss of function, and nephritis. How far these bad results are due to the drug and how far to the disease is as yet uncertain, but it seems established that in persons who have undergone a course of treatment with some other arsenical compound the nerves become more susceptible and the use of salvarsan may give rise to optic atrophy.

A number of conditions of the system render the remedy especially dangerous. Among these may be mentioned wide-spread degenerations of the central nervous system, myocarditis, arterial diseases, especially aneurism, advanced nephritis, diabetes mellitus, and gastric ulcer.

The experience of clinicians up to the present time would seem to justify the following conclusions concerning the value of salvarsan in syphilis: (1) In cases in which none of the contra-indications are existent it is a remedy of great value, producing at least amelioration in 90 per cent. of the cases and probably complete and permanent cure in a considerable number. (2) Its employment is not without danger and should be undertaken only under favorable conditions for observation of the patient and by those sufficiently expert to follow carefully a somewhat elaborate technique. (3) The drug should not be relied on exclusively, but should be followed by a course of mercurial treatment. (4) It is of no value for the relief of so-called parasyphilitic conditions, such as locomotor ataxia, which are not due directly to the spirochætæ, but are the evidences of past ravages of the parasite.

Although chiefly employed in syphilis, the drug has been used in various other diseases due to protozoa, with, in some instances, equally beneficial results. In relapsing fever it has proven of great service. It has also been tried in malaria and in pellagra, but there is no convincing evidence of its value in these conditions.

Administration.—Salvarsan may be administered either intramuscularly or intravenously. The latter method seems to be the more efficacious, but is also more likely to be followed by evil results if not given with perfect technique. As already remarked, the drug appears commercially in the form of a hydrochloride, which is highly acid and, therefore, locally irritant. Although it has been employed in the original state, the bulk of authority indicates that it is desirable to give it either as a neutral suspension or as an alkaline solution; for intravenous injection the latter should always be employed. For intravenous injections the dose should be diluted with about 300 mils (9 ounces) of normal salt solution. It is needless to point out that the injection must be carried on with absolute asepsis. Special apparatus is desirable, several forms being on the market for the purpose. To obtain the best results give two injections at an interval of one or two weeks.

Neosalvarsan is given in a similar manner, except that being readily soluble in water it does not require the addition of an alkali. The solution should be freshly made, as it decomposes rapidly when exposed to the air.

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Heffter ..... A.E.P.P., 1901, xlvi.

MERCURY.

Materia Medica.—Metallic mercury in its ordinary form is almost incapable of absorption, but when finally divided by trituration with inert substances it becomes capable of penetrating the mucous membranes. Preparations containing metallic mercury which are recognized by the United States Pharmacopœia are: the mass of mercury, the mercurial ointments, and mercury with chalk. Mercury is capable of acting either as a univalent or as a divalent base, consequently it

forms two series of salts, the mercurous and the mercuric. The Pharmacopœia recognizes of the salts of mercury—two chlorides, two iodides, two forms of the oxide, an oleate, and a complex body resulting from the precipitation of solution of corrosive sublimate by ammonia known as ammoniated mercury.

Mercurous chloride or calomel (*hydrargyri chloridum mite*) occurs as a white crystalline powder, insoluble in water, alcohol, or ether. *Mercuric chloride* or bichloride of mercury, more commonly known as corrosive sublimate (*hydrargyri chloridum corrosivum*), is in colorless crystals, soluble in thirteen parts of water and three parts of alcohol, odorless, but with an acrid metallic taste.

Mercurous iodide, or yellow iodide of mercury, is a bright yellow amorphous powder without odor or taste, practically insoluble in either water or alcohol. *Mercuric iodide,* or red iodide of mercury, is a bright-red, odorless, and tasteless powder, sparingly soluble in alcohol and practically insoluble in water; solutions of potassium iodide, however, dissolve it easily.

Mercuric salicylate is of a yellowish or pinkish color, practically insoluble in water or alcohol, but is soluble in alcoholic solutions. It is generally administered in oily suspension by intramuscular injection.

Two forms of the oxide of mercury are recognized, the yellow and the red. In their chemical relations these two preparations do not differ. They are both insoluble in alcohol and in water. The yellow is amorphous and of a light orange-yellow color; the red is composed of orange-red crystals which become yellow when finely triturated.

Ammoniated mercury is made by precipitating the bichloride with ammonia water, and has the formula $HgNH_2Cl$. It occurs in the form of a white, amorphous powder, with a metallic taste, insoluble in water or alcohol.

Incompatibilities.—The incompatibilities of corrosive sublimate are very numerous. It forms insoluble salts with all the phosphates, sulphates, carbonates, and hydroxides. Iodine and the iodides precipitate from the solution of mercuric chloride the red iodide of mercury, but an excess of the iodide forms a double potassio-mercuric iodide, which redissolves, giving a colorless solution. Corrosive sublimate also precipitates most of the alkaloids. It is likewise incompatible with albuminous matters.

Official Preparations:

Hydrargyrum .....Not used internally.
Hydrargyrum Ammoniatum [White Precipitate] .....Not used internally.
Hydrargyrum cum Creta [Gray Powder] .....2 to 10 grains (0.13–0.6 Gm.).
Hydrargyri Chloridum Mite [Calomel] ..... { Alterative ½ to 1 grain (0.03–0.06 Gm.). Cathartic 2 to 10 grains (0.13–0.6 Gm.).
Hydrargyri Chloridum Corrosivum [Corrosive Sublimate]....1/20 to ⅛ grain (1–8 milligm.).

Toxitabellæ Hydrargyri Chloridi Corrosivi (Each contains 0.5 Gm.). External use.
Hydrargyri Iodidum Flavum [Protiodide] ..... ⅙ to 1 grain (0.01–0.06 Gm.).
Hydrargyri Iodidum Rubrum [Biniodide] .....1/60 to ⅛ grain (1–8 milligm.).
Hydrargyri Oxidum Flavum.....Not used internally.
Hydrargyri Oxidum Rubrum....Not used internally.
Hydrargyri Salicylas .....1/30 to ⅛ grain (2–8 milligm.).
Massa Hydrargyri [Blue Mass]..1 to 10 grains (0.06–0.6 Gm.).
Unguentum Hydrargyri [Blue Ointment] (50 per cent.).....Externally only.
Unguentum Hydrargyri Dilutum (30 per cent.).....Externally only.
Oleatum Hydrargyri .....Externally only.
Unguentum Hydrargyri Ammoniati (10 per cent.).....Externally only.
Unguentum Hydrargyri Nitratis (7 per cent.) [Citrine Ointment]Externally only.
Unguentum Hydrargyri Oxidi Flavi (10 per cent.).....Externally only.
Pilulæ Catharticæ Compositæ....1 to 2 pills.

Physiological Action.—*Local Action.*—The local effect of mercurial preparations varies from complete inertness to an active escharotic influence, so that each preparation must in this regard be studied by itself.

The soluble forms of mercury are active precipitants of albumin and consequently poisonous to all forms of protoplasm. They appear to be especially toxic to lower forms of life, and are powerfully germicidal. (For consideration of the antibacterial action of mercury see page 345.) The albuminate of mercury is soluble in an excess of albumin and, therefore, does not act as a protective coating for the underlying tissues as do the coagula formed by the astringents. For this reason strong solutions of such salts as the bichloride or nitrate of mercury exercise a caustic action.

Absorption and Elimination.—All the official preparations of mercury yield themselves, or the mercury in them, to absorption. The metal has been found in the blood, in the urine, in the serum of blisters, in the saliva, in the fæces, in the pus from ulcers, in the seminal fluid, in the milk of nursing women—indeed, in every conceivable secretion and in every tissue, even in the aborted fœtuses of salivated women. There has been much speculation as to the form in which mercury is absorbed. It is evidently not in the form of corrosive sublimate, as was at one time believed, as this is a powerful precipitant of albumins. There are two theories to-day, each of which has its adherents. One is that it is converted into an albuminate of mercury which is kept in solution by the excess of albumin; the other that an oxide is formed in the intestines which is soluble in fats.

After absorption the elimination of mercury is shared in by nearly all the glands of the system, but especially the kidneys, the salivary glands, and the glands of the intestinal tract. Although the single

dose of mercury does not remain long in the system, when the drug is administered constantly for a length of time elimination does not keep pace with absorption, so that the metal accumulates in the tissues. Moreover, elimination takes place irregularly and intermittently, for reasons that at present cannot be made out. Further, there does not appear to be any limit of time during which stored-up mercury may remain in the body; indeed, all the evidence points to the possibility of mercury being deposited in the tissues in such form that it is practically inert and has no influence upon the system, liable, however, under certain agencies, to be set free and to exert its power upon the general nutrition.

Secretion.—Mercury being a local irritant during the course of its elimination by glandular structures, it may lead to an increased secretion of various glands of the body if the dose has been sufficiently large to irritate and not large enough to be destructive to the glandular protoplasm. Apparently among the most susceptible glands of the body are the salivary, and even relatively small doses may lead to salivation or ptyalism. If the dose is large there are also inflammatory changes in the mucous membrane of the mouth and eventually even ulceration.

It seems probable, however, that it has an action upon the kidney which is of a different type from that upon the other glands of the body. If the statement of Fleckseder that the diuresis begins before the mercury can be detected in the urine be true, it is evident that its effect can not be due to a local irritation. Fleckseder believes that it acts by causing a hydræmia of the blood. When given in toxic quantities, however, mercury causes inflammatory changes in the kidneys. According to Hedinger the tubercular cells are the most susceptible, the glomeruli being affected comparatively late.

The diarrhœa which is caused by many salts of mercury is the result of a local irritation of the intestinal glands. When the insoluble compounds are used it is probable that this inflammatory change is the result of a local action, but it is worthy of note that diarrhœa may follow the introduction of mercury into the system through other channels, the glands of the intestines being irritated by the metal during their effort at elimination. An interesting observation in this connection is that of Gola that there is an equilibrium between the renal and intestinal irritation; that is, that after toxic doses, if the kidneys are stimulated to great excretion, the intestinal action is comparatively slight, and *vice versa.*

Blood.—In small doses mercury appears to act as a stimulant to the blood-making organs, an increase in the number of corpuscles and hæmoglobin having been reported in the lower animals, as well as syphilitic and healthy men. When, however, toxic quantities are given the blood becomes anæmic, apparently through a destructive action upon the erythroblastic cells of the bone-marrow, although there is reason to believe that there is also increased destruction of the red corpuscles.

It has also been shown that in mercurial ptyalism there is a diminu-

tion not only in the red corpuscles but also in the fibrin content of the blood. What the effect of small doses upon the blood fibrin is we have no definite knowledge, but its clinical usefulness in cases of fibrinous exudations would indicate that even in therapeutic quantities a similar effect is exercised.

Nutrition.—A sharp distinction must be drawn between the effects of therapeutic and toxic doses upon the nutritive processes. In small quantities it appears to exercise a favorable influence on the metabolism similar to that shown by arsenic, for it has been shown that not only is the blood enriched by the use of proper doses of mercury, but that there is also a gain in body weight.

Therapeutic Uses.—Mercury is used in medicine for five purposes: (1) as an antiphlogistic, (2) as an antisyphilitic, (3) as a cathartic, (4) as a diuretic, (5) as an antiseptic (see page 346).

Antiphlogistic Uses.—The use of mercury in inflammatory conditions originated with Robert Hamilton in the latter part of the eighteenth century, and soon became universal in England and in America. As is well known, an increase of hæmic fibrin is one of the most characteristic effects of inflammation, and if, as there is reason to believe, mercury lowers the fibrin content of the blood, its value as an antiphlogistic is easily comprehensible. But it must be confessed that the proof of its usefulness is to be found chiefly in the results which have followed clinically its employment in these conditions. Although much of the clinical evidence is lacking in desirable accuracy, the mass of testimony is so enormous that it overrides the probability of fallacy. Some have objected to the sort of clinical evidence which has been deduced as to its value in these conditions that a possibly latent syphilis has not been excluded. While this is in a measure true, it is incredible that any such explanation could apply to the enormous number of cases in which it has been observed.

There is one inflammatory affection—iritis—which from its anatomical relations is completely visible at all stages, and it is noteworthy that of all types of inflammations the belief of clinicians as to its value is firmest in this affection. Oculists are unanimous in their opinion as to the value of internal use of mercury in the treatment of iritis, whether of syphilitic or other origin.

The chief value of mercury as an antiphlogistic is seen in inflammatory conditions of the endothelial membranes, especially when there is fibrinous exudate, as in pleurisy, pericarditis, and peritonitis. In endocarditis, while its utility is open to doubt, it is so extremely important, if possible, to prevent exudation that since we know of no other agent which has this effect, mercury should be administered freely at once.

In inflammatory conditions of the mucous membranes mercury is of less value, but appears at times to exercise some favorable influence, and has been widely used in the treatment of inflammatory conditions of the throat, even in diphtheria, with asserted benefit. Its value in

enteritis depends probably more on its antiseptic and cathartic action than on any antiphlogistic influence.

When mercury is used in the treatment of inflammations it should be administered in the stage of exudation and given freely to the verge of ptyalism; in many cases it is necessary to combine it with opium to guard against the excessive action of the bowels. It should not be employed in adynamic conditions or where the exudate is serous rather than fibrinous.

Antisyphilitic Uses.—Although it has not been definitely proven, our knowledge of the effects of mercury on lower forms of animal life, as well as the character of the results which follow its use in syphilis, renders it extremely probable that its beneficial influence in this disease is brought about through a destructive action on the spirochæta pallida. If this be the true mode of its action it is evident that the greatest benefit from the drug is to be expected in the earlier stages of the inflammation, a conclusion which is abundantly confirmed by clinical experience. While there is some difference of opinion among syphilographers, the bulk of authorities believe that if the use of mercury be commenced early enough and continued long enough most cases can be completely cured; that is, so that there will be no late tertiary lesions.

The author believes that mercury should form at least part of the treatment of practically every case of syphilis which is seen in either the primary or secondary stage, no matter what other treatment may be employed in conjunction with it; there may possibly be rare instances of idiosyncrasy which prevent the use of the drug, but these are extremely uncommon if existent. There will, of course, occasionally be seen cases in which the mercurials cannot be employed immediately, but with proper preparatory treatment these cases can nearly always be given a thorough course.

The administration of mercury should under ordinary conditions be commenced immediately after a positive diagnosis has been made. If it is possible, either from the character of the initial sore or by means of the Wassermann test or any other means, to make a certain diagnosis before the appearance of the secondary lesions, there should be no delay in beginning the treatment. In many cases, however, it is impossible to make more than a provisional diagnosis before the appearance of the skin symptoms, and in such a case it may be advisable to withhold the drug until this time, as otherwise a positive diagnosis may never be made. In the ordinary case, in the beginning of the treatment, it is usually advisable to push the mercury to the point of mild pytalism, after which it should be continued in smaller doses. Under ordinary circumstances the mercurial course should be maintained persistently for at least two years and until the Wassermann test is negative.

In the tertiary stage, if the Wassermann test be positive, mercury is indicated, but for the parasyphilitic manifestations it is probably of

little, if any, value. The occurrence of a gumma is an evidence that the infection still persists and demands active mercurialization.

The various methods of exhibiting mercury in syphilis are considered under the title of Administration (see page 304).

Cathartic Uses.—The purgative action of mercury depends upon a local irritation of the mucous membrane of the bowel, probably increasing both secretion and peristalsis. The only preparations of mercury which are used to any considerable extent as purgatives are calomel and blue mass. Of these the first is by far the more reliable.

The chief interest in the purgative action of mercurials centers in the question as to their influence upon the liver. Clinically, there seems no room for doubt that mercurials are capable of increasing the bile in the intestinal tract, especially in certain conditions, such as that known as biliousness or hepatic torpor, in which this excretion is lacking. The researches of Stadelmann and his pupils, and of Pfaff and Balch, seem, however, to have conclusively proven that mercury has no influence upon the formation of bile in the liver.* The appearance of bile in the stool in these cases is probably due to an antiseptic influence preventing the decomposition of the bile by bacteria, and, perhaps, also to some reflex effect upon the muscular walls of either gall-bladder or the bile-ducts leading to the forcing out of preformed bile into the duodenum.

The mercurial purgatives are employed, especially where an absence of bile in the intestinal tract is shown by the color of the alvine discharges; the occurrence of the so-called clay-colored stools, whether loose or costive, indicates a mercurial purgative. It is to be remembered, however, that where the lack of bile depends upon an obstruction in any portion of the gall-ducts, whether due to the presence of a calculus or to an inflammatory swelling of the mucous membrane of the bile passages, mercury cannot force its appearance in the intestinal tract. However, in cases of catarrhal jaundice the mercurials are often serviceable, not so much by their cholagogic influence as by their antiphlogistic action.

Mercurial purgatives are also of much value in various types of intestinal inflammations, especially those of bacterial origin. Their action here is due, first, to the purgative action which mechanically dislodges the irritant; secondly, to their antiseptic powers, and, thirdly,

* In passing it may be stated that at present the only agents which are known to affect the quantity of bile secreted are the bile-salts and the salts of salicylic acid, although there is some evidence that sodium benzoate and colchicine have some influence in this direction. Concerning the action of bile-salts upon the liver, while there is much experimental evidence to show that oxgall is the most powerful stimulant we have to the secretory activity of the liver, Schaeffer believes that this substance does not have a direct stimulant action upon the liver, but that its effects are due simply to the offering for absorption a preformed constituent of the bile, because he found that the amount of bile solids passed out after the exhibition of oxgall did not exceed the normal plus the amount which had been artificially exhibited.

to their antiphlogistic influence. Because of its antiseptic action calomel is useful not only in true enteritis, but in small non-purgative doses, as in intestinal fermentation, as an antiseptic.

Diuretic Uses.—Mercury has been used for many years with success as a stimulant to the kidney. It is at present doubtful whether the increased secretion is the result of an irritant action on the renal epithelium or of changes in the composition of the blood. But whichever it may be, as life cannot long continue after renal failure, it is often necessary to continue functional activity of the kidney, even at the risk of adding to the irritation. In chronic parenchymatous nephritis, with alarming decrease in secretion of urine, mercury is one of the most effective diuretics known. In cardiac dropsies it often exercises a beneficial action, not only in evacuating the effusion but also for its effect on the digestive organs. While apparent benefit has in some cases of cardiac dropsy resulted from the continued use of minute doses of mercury, if it is desirable to produce a marked diuretic effect large quantities of the drug are administered. If a very prompt action is required, as in acute suppression of urine, five grains of calomel may be administered every two hours until fifteen grains are taken, guarding against purgation, if necessary, with the conjoint use of opium. Under ordinary circumstances, one-quarter grain may be given every two hours until there is beginning salivation, or tenderness of the teeth on biting.

Administration.—As a cathartic, the most serviceable form of the mercury is the mild chloride, which may be given in doses of from one-tenth to one-fourth grain every half hour until twelve doses are taken. From a fear of the formation of corrosive sublimate in the stomach the direction is frequently given that no acid drinks should be taken after the ingestion of calomel. There is absolutely no foundation for this superstition; calomel may be converted into corrosive sublimate by boiling hydrochloric acid, but such change cannot possibly take place in the stomach. Moreover, the common practice, which apparently has arisen from this fear, of combining sodium bicarbonate with calomel for the purpose of preventing the formation of the bichloride defeats its own object, for when these tablets are kept for a length of time, especially if exposed to dampness, there is a chemical change taking place with the formation of corrosive sublimate and liberation of metallic mercury. The tendency of mercurial cathartics to gripe may be prevented by the addition of small doses of belladonna.

As an antiphlogistic, either of the chlorides or iodides may be administered in fractional doses.

In cases of syphilis it is generally desirable to push the mercury to complete saturation of the system; that is, to keep the patient in a condition just below salivation. This may be accomplished in various methods. That most frequently employed, because most convenient, is the administration of the mild chloride or yellow iodide in doses of from one-fourth to one and one-half grains (0.015–0.030 Gm.) three

or four times a day, gradually increasing the dose if the patient can stand it. The combination of small doses of potassium iodide is useful to prevent the deposit of insoluble compounds of mercury in the internal organs.

In cases where the alimentary tract refuses to accept the necessary amount of mercury it may be introduced into the system through the skin. In practising inunctions it is essential to remember that when mercury is applied to a hairy surface it is very prone to cause a troublesome irritation, due to inflammation about the hair-follicles. Indeed, the continuous application of the mercurial to almost any surface of the body will cause finally an eczematous eruption. Further, when the skin is in thoroughly good condition it absorbs much better than when it is irritated. The frequent use of the hot baths seems also to aid in the absorption, and possibly also in the elimination of the mercury; and the good effects obtained at the Arkansas and other thermal springs largely depend upon the frequent employment of the hot bath with the free use of the mercurial. It is therefore usually better to have the inunction practised in the evening, after the patient has had a prolonged bath; and in cases of great urgency the baths may be repeated two or three times a day, so as to produce free sweating, and the inunction practised, it may be, twice a day. In order to avoid irritation of the skin, a regular order should be maintained in the application, as follows: *first day,* inner side of both upper arms; *second day,* inner side of both thighs; *third day,* inner side of both forearms; *fourth day,* inner side of both legs; *fifth day,* upon both groins; *sixth day,* upon the back; *seventh day,* recommence the series.

The advantage of inunction is that the digestion is less apt to be disturbed than when the drug is exhibited by the mouth; the disadvantages are the greater or less publicity which it entails, the trouble which it involves, its apparent dirtiness, and the uncertainty of dosage. In private practice it is rarely employed except in the case of infants, when the mercurial ointment is rubbed into the abdomen and armpits, or often simply smeared upon the flannel roller or binder which usually envelops the body.

In severe forms of syphilis which do not yield to the foregoing methods of treatment benefit may frequently be derived from the hypodermic use of the drug. A number of preparations have been suggested for this purpose, but my own preference is for the aqueous solution of corrosive sublimate. From one-sixteenth to one-eighth of a grain of bichloride should be injected deeply into the muscles of the back or of the thigh daily or every other day, according to the needs of the case, care being exercised to see that the part is well rubbed immediately after the injection, so as to dispel the local accumulation of fluid, and that injections are not given on successive days in places near to one another. In some cases very pronounced pain is produced. This can be overcome, however, by injecting one-

fourth grain cocaine immediately before the injection of the mercurial into the same spot. My own practice is to dissolve one-fourth grain of cocaine hydrochloride in fifteen or twenty minims of water, inject it into the lumbar muscle, then detach the syringe from the needle, leaving the latter in the muscle, and after rinsing the syringe with sterile water fill it with the one-half per cent. solution of corrosive sublimate, reconnect with the needle, and inject into the spot which has been anæsthetized with the cocaine.

Many prefer, for hypodermic injection, an insoluble salt of mercury because the injection is less painful and because, being more slowly absorbed, it is not necessary to give the injection at such frequent intervals. Of the official preparations the best for hypodermic injection is probably calomel, which may be given suspended in a mixture of equal parts of glycerine and water in doses of one grain once or twice a week.

Formerly mercury was sometimes administered by fumigation, but as this practice has nothing to recommend it and has largely gone out of vogue, it is hardly necessary to describe it. The principle of the method was the vaporizing of the mercury, which deposited in minute globules upon the skin.

Toxicology.—It is necessary to recognize two forms of mercury poisoning—that which is produced by single large doses of a soluble salt, and that which is the result of long-continued use of any mercurial.

Acute poisoning is most commonly produced by the antiseptic tablets of corrosive sublimate. The symptoms are due to violent irritation of the gastro-intestinal tract and of the kidneys, and their severity is generally proportional to the dose ingested. The first symptom is a peculiar metallic taste immediately on swallowing the poison or shortly afterwards. This is soon followed by a burning sensation in the epigastrium, with nausea and vomiting, the vomitus being at first mucous, then bilious, and finally bloody. Later there is severe abdominal pain and tenderness, with profuse purging, at first serous in character but afterwards affording small mucous bloody stools, which are often voided with much straining. The breath generally becomes fetid. If the patient survives for more than a few hours the urine becomes scanty, with large amounts of albumin, numerous tube casts, and often blood. Death may occur in the course of two or three hours with symptoms of collapse, or may be postponed for ten or twelve days. In the latter cases a petechial eruption may appear and salivation sometimes, but not always, occurs. Frequently there are violent ulcerative processes in the mouth and throat. When recovery occurs the convalescence is likely to be slow.

In the treatment of corrosive sublimate poisoning the most important factor is the prevention of absorption. Some form of albumin, as white of egg, milk, or hashed meat, may be given as an antidote,

but even if the patient has vomited it is well to wash out the stomach thoroughly with tepid water. The subsequent treatment will be varied according to the individual conditions. If the pain be severe, morphine in some form will be injected. For the diarrhœa, tannic acid or bismuth may be combined with the opiates. Demulcent drinks, as of acacia or albumin water, for the soothing of the gastric inflammations, are sometimes of service. The administration of large quantities of water, either hypodermically or through the colon, is recommended on the ground that by diluting the poison it will lessen the irritation of the kidney. If symptoms of kidney failure supervene, sweat-baths may be combined with hypodermoclysis.

A form of subacute poisoning is sometimes seen in which the most prominent symptom is irritation of the kidney. A number of cases of this type of intoxication have followed the use of vaginal douches.

The symptoms of *chronic mercurial poisoning* are very similar for all preparations. In the mildest degree, which may be considered as the therapeutic limit, these symptoms consist of slight fetor of the breath, some soreness of the teeth when knocked forcibly together, and perhaps an increase in the flow of the saliva. If the use of mercury be persisted in, the gums become swollen, soft, and spongy, bleeding on very slight abrasion, and there is a decided increase in the secretion of saliva. Beyond this point the therapeutist is never justified in carrying the use of the drug. If it be done, the local symptoms in the mouth increase in severity, the tumefied gums become inflamed and marked by a dark red line at the junction of the teeth; the tongue is swollen, sometimes enormously, protruding from the mouth; the teeth are loosened in their sockets; the saliva is enormously increased in quantity and altered in quality, forming great, ropy, viscid masses, which pour over the thickened lips; the parotid glands, and even the submaxillary, are very much enlarged and tender. Severe ptyalism may be accompanied by marked fever, and nephritis is a not uncommon occurrence. Loss of the teeth, extensive ulceration of the soft parts, and even necrosis of the jawbones have occurred, and death from exhaustion resulted, or the patient struggled through to recovery, seamed and disfigured for life. During severe ptyalism emaciation goes on rapidly, and seems to especially affect imperfectly organized tissues, so that exudations very generally rapidly disappear. The blood suffers very decidedly, becoming more fluid and watery than normal and having its power of coagulation impaired.

In a number of cases there have been various anomalous manifestations of the mercurialism. Various types of cutaneous eruptions, the most common of which is a slight erythema, have been ascribed to its use. In a number of cases it has given rise to various forms of peripheral neuritis, and cases simulating chronic lead poisoning with wrist-drop have been described.

In the treatment of mercurial ptyalism the most important measure is the local hygiene of the mouth. Antiseptic astringent mouth washes

should be used at frequent intervals. Atropine may be given internally to check the excessive secretion. The internal use of potassium iodide should be avoided, since by converting the mercury which is deposited in the internal organs into a more soluble form it will increase the amount of the metal in the blood stream and add to the irritation of the eliminating organs. In cases, however, where the poisoning has manifested its effect chiefly upon the nervous system it is essential to hasten its elimination, and the use of potassium iodide is to be recommended for this purpose.

IODINE.

Materia Medica.—Iodine is recognized by the United States Pharmacopœia both in the form of metallic iodine and in the form of hydriodic acid and many of its salts. It is a soft, friable, opaque substance, occurring in crystalline scales with a semi-metallic lustre and of a bluish-black color. Its odor resembles that of chlorine; its taste is hot and acrid. It is somewhat volatile at ordinary temperatures, but when heated to 237.2° F. melts and emits the beautiful purple or violet vapor to which it owes its name. It is freely soluble in glycerine, alcohol, and ether, but requires five thousand times its weight of water to dissolve it. With starch it strikes a deep blue color, and this test is so delicate that it will indicate the presence of iodine in four hundred and fifty thousand times its weight of water. In testing animal liquids, such as urine, for iodine, a small quantity of nitric acid should be added to insure its being free in the liquid.

Absolute *hydriodic acid* is a gaseous substance, a ten per cent. solution of which is recognized by the United States Pharmacopœia under the name of diluted hydriodic acid. This is a clear, colorless fluid, with an acidulous taste. The iodides of sodium, potassium, strontium and ammonium are official. They are all white crystalline salts, freely soluble in water and having a salty, somewhat bitter, taste. They are all more or less deliquescent.

Iodine and the iodides form insoluble compounds with most of the alkaloids, with the salts of silver, lead, and mercury.

Official Preparations:

Iodum	Not used internally.
Tinctura Iodi (7 per cent.)	External use only.
Liquor Iodi Compositus [Lugol's Solution] (Iodine 5 per cent.; potassium iodide 10 per cent.)	5 to 10 minims (0.3–0.6 mil).
Unguentum Iodi (4 per cent.)	External use.
Acidum Hydriodicum Dilutum (10 per cent.)	15 to 20 minims (1–1.3 mils).
Syrupus Acidi Hydriodici (1 per cent.)	1 to 2 fluidrachms (4–8 mils).
Ammonii Iodidum	3 to 20 grains (0.2–1.3 Gm.).
Potassii Iodidum	3 to 20 grains (0.2–1.3 Gm.).
Sodii Iodidum	3 to 20 grains (0.2–1.3 Gm.).
Strontii Iodidum	3 to 20 grains (0.2–1.3 Gm.).

Physiological Action. — *Local Action.* — Metallic iodine, when applied to any part of the body, acts as a very powerful irritant, or,

if in highly concentrated form, as a mild caustic. The tincture stains the skin yellow, and causes, if applied with sufficient freedom, smarting, some erythematous inflammation, and finally desquamation. Its repeated application blisters and destroys the cuticle. Upon mucous membranes its action is more intense than upon the skin.

Iodine in the elemental state is a powerful germicide. According to Goebel, a one to one thousand solution will destroy the *staphylococcus pyogenes aureus* in one minute and a one per cent. solution the anthrax spores in five minutes. Other authorities, however, do not find it quite so powerful; according to Sternberg, for example, it requires two hours for a one to five hundred solution of iodine to destroy staphylococci. It seems certain, however, that iodine is three or four times as powerful a germicide as phenol.

General Effects.—The iodides in single dose are almost without effect upon the system. In very large quantities they will exercise a salt action, but they are scarcely more toxic than the chlorides.

The belief which is held by a few, that the iodides dilate the blood-vessels, is absolutely without any foundation; neither pharmacologic experiments nor clinical observations support this supposition.

When used for long periods of time the iodides appear to increase the rapidity of nitrogenous catabolism and may lead to loss of weight. It has been suggested that this action is the result of stimulant effect upon the thyroid gland. In favor of this view are the facts that in conditions of hyperactivity of the thyroid, as in Graves's disease, the administration of iodides often produces an aggravation of the symptoms; that the exhibition of iodides increases the resistance of mice to aceto-nitrile, a reaction which Hunt believes is characteristic of thyroid secretion. On the other hand, in normal individuals even large doses of iodine do not produce the characteristic symptoms which are brought about by thyroid feeding.

In certain diseased conditions the effects of the iodides are much more marked than in healthy individuals; thus in cases of leprosy or tuberculosis a febrile reaction may follow the injection of potassium iodide. The explanation offered by Sorel of these phenomena is that the iodide reacts with certain antibodies produced by the disease, forming a ferment which dissolves certain proteins, as those which form the tuberculous lesion. Jobling and Petersen believe that the effects in syphilis and tuberculosis are due to increased autolysis brought about by the iodine combining with an antiferment which is found in the local lesions.

Chronic iodic intoxication, or iodism, may manifest itself in several ways. The most common symptoms are dull pain in the region of the frontal sinus, coryza, sore throat, ptyalism, and an eruption upon the skin, which is usually an acne, but may take almost any shape. In its serious forms it becames pustular or bullous, and may be accompanied by violent constitutional disturbances.

By some it is believed that the symptoms of iodism are the result

of local irritations of glandular structures due to the liberation of free iodine during excretion by these structures.

Absorption and Elimination.—The salts of hydriodic acid are absorbed rapidly and escape promptly unchanged. When elemental iodine is exhibited internally the greater part of it appears to be absorbed as an iodide, although some of it circulates as an organic combination of iodine. The effects upon the system, therefore, of iodine are the same as those of hydriodic acid and its salts.

Therapeutic Uses.—The iodides have been employed as alteratives in an enormous variety of conditions. In fact, there is probably no chronic disease in which they have not been recommended. Nearly all of those conditions in which the iodides have proven beneficial are accompanied with the outpouring of fibrinous exudate or the overgrowth of connective tissue. From this clinical fact it would seem only natural to conclude that their value depended upon some power of softening and causing the absorption of fibrin. It must be confessed, however, that there is no experimental proof of this action although it is a well-established clinical fact that they may increase the breaking down and absorption of exudate in certain chronic inflammatory conditions. Thus, for example, tubercular lymph-glands will often begin to suppurate under the administration of iodides; a quiescent lesion in the lungs may be converted into an actively progressive one by the injudicious use of the remedy. By many it is believed that their favorable influence in syphilis is due simply to this softening action upon the lesions which are characteristic of the tertiary stage of this disease. The evidence that they will cause absorption of true fibroid tissue is, however, much less convincing, and although they are widely employed in various sclerotic conditions, as arteriocapillary fibrosis, fibroid nephritis, and similar conditions, it is doubtful whether this use is of any real benefit. In chronic scleroses of the central nervous system, such as locomotor ataxia, the iodides are habitually administered in large doses, sometimes apparently with beneficial results, but generally without causing any material change in the condition.

In tuberculosis the iodides are ordinarily contra-indicated, since they tend to lead to the absorption of the inflammatory exudate which may be walling off a lesion and thereby change what is practically an arrested disease into a progressive one. It is a common experience to find in a case of pulmonary tuberculosis in which the sputum examinations have been repeatedly negative the expectorations swarming with tubercle bacilli after the free use of iodide; indeed, the administration of iodides is sometimes employed for diagnostic purposes, although the risk of increasing the activity of the lesion would seem hardly to justify such a usage. In scrofulous lymph-glands, however, where for any reason it is impossible to operate, they are sometimes used to increase the breakdown of the fibroid tissue, with the idea that the materies morbi may be extruded from the system through free suppuration.

The most certain effects from iodides are seen in syphilis. So far as our present evidence goes, they do not have any action whatsoever upon the spirochæta and are, therefore, of no service to check the advance of the disease in its early stages. They do, however, appear to exercise a powerful influence upon certain of the lesions which are formed, especially the lesions of the so-called tertiary stage. The iodides are further useful, however, in this disease because they tend to keep the mercury salts in solution. As is well known, when mercury is used continuously for long periods of time it tends to be stored up in certain internal organs where, of course, it cannot exercise its beneficent destructive influence on the spirochætæ. Potassium iodide, probably by the formation of double iodide of mercury and potassium, will cause those stored by mercury to be dissolved by the circulating fluids and once more appear in the blood. This influence is so powerful that the free administration of potassium iodide may give rise to mercurial ptyalism even after the cessation of the administration of mercury.

In actinomycosis the iodides appear to exercise a specific influence. How they act we have absolutely no knowledge.

In chronic rheumatic conditions there is considerable evidence of the value of the iodides. It is probable that their effect is due to the softening of inflammatory exudates, for in acute rheumatism or rheumatic fever they are without effect.

The iodides notably increase many secretions. This effect is due not merely to their salt action, but is apparently the result of a direct influence on glandular structures. Attention has already been called to the theory that this action is due to the liberation of free iodine, which acts as an irritant to the gland. Among the glands most markedly affected are those of the bronchial mucous membrane. For this reason the iodides are valuable remedies in certain types of bronchitis in which there is diminished secretion, and especially when associated with asthma. Upon the asthmatic paroxysm the iodides are entirely without influence, but there is probably no one drug so generally useful to prevent the occurrence of these attacks.

In chronic inflammatory conditions of the serous membranes with the formation of fibrinous exudates, as in chronic pericarditis, chronic pleurisy, and the like, the iodides are remedies of much value.

Certain salts of hydriodic acid form with many metals double salts which are freely soluble; therefore, in chronic metallic poisonings they lead to the liberation of any of the metal which may be stored up in the system and hasten excretion. Often this effect is of therapeutic importance, especially in chronic lead poisoning. It must be remembered, however, that the increase of the metal in the circulating blood may lead to an exaggeration of the symptoms. Especially is this liable to be the case in mercurialism, but the author has seen a furious attack of cerebritis occur after the free use of iodides for the relief of ordinary lead colic.

Local Uses.—Iodine is used locally as a counterirritant and as an antibacterial. As a counterirritant iodine is useful wherever it is desired to maintain a mild persistent influence; the tincture of iodine is perhaps the most popular of all local applications for inflamed joints, whether due to injury or some diathesis. It is also useful for the purpose of combating chronic inflammations of deep-seated origin.

As a germicide iodine has in the past been much neglected; within the last few years, however, surgeons have begun to use it widely for the purpose of sterilizing the skin at the seat of operation. It has been abundantly shown that simply painting the skin with a 10 per cent. solution of iodine in alcohol renders it completely sterile. The great value of iodine for this condition lies not only in the fact that it ranks among the most powerful of our germicides, but also that, being partially volatile at the body temperature, it penetrates beneath the epidermal layer. In practical disinfection of the skin it should be remembered that alkaline soaps will convert metallic iodine into an iodide, and that the latter are entirely without disinfectant value; therefore, it is necessary to thoroughly wash all soap from the surface before the application of the disinfectant. As a disinfectant and stimulant iodine is also of great service in chronic inflammatory conditions, such as chronic pharyngitis, ozœna, vaginitis, sluggish ulcers, and other similar conditions. In cases of retraction of the gums it acts both as an antiseptic and as a stimulant.

IODOFORM.

Iodoform, which was discovered by Serullas in 1822 and introduced into medicine by Glover in 1837, is a triiodo-methane (CHI_3), and, therefore, chemically homologous to chloroform. It is formed when iodine is heated with alcohol in the presence of an alkali. It occurs as a greenish-yellow powder with a very powerful and persistent odor; practically insoluble in water, but readily soluble in ether and the fixed oils.

Official Preparations:

Iodoformum	3–5 grains.
Unguentum Iodoformi (10 per cent.)	External use.

Physiological Action.—Notwithstanding the fact that iodoform, when introduced into the general system, acts as a violent poison, and notwithstanding numerous experiments upon the lower animals, our knowledge of its effects upon the system is unsatisfactory. A large proportion of the iodoform ingested is destroyed in the stomach, escaping as an iodide or as an iodate, but a proportion of it circulates as probably a new albuminous compound of iodine, and it is certain its toxic effects are very different from those of the iodides. Its elimination is so slow that it can be detected in the urine three days after the administration of a single dose.

In the frog iodoform produces a muscular relaxation and

paralysis. In dogs and cats it produces anæsthesia and narcosis, associated sometimes with convulsions, with rapid or irregular respirations and slow, feeble pulse. In rabbits, however, it does not appear to cause narcosis. In man the symptoms, as recorded, have been very various. They may be preceded by general malaise for a day, and then suddenly burst forth. In the most characteristic and severe class of cases the phenomena resemble somewhat those of meningitis, and may be somnolence, deepening into stupor, with contracted, motionless pupils, or restlessness, ending in active delirium, in either case the temperature being normal and the pulse exceedingly rapid. A peculiarity of these cases seems to be that death usually follows, although the symptoms have developed abruptly and the dressings have been removed at once (see Schede). A roseola-like dark red eruption has been noted in some cases of poisoning. Convalescence may be very protracted, the patient remaining unconscious or semi-conscious for some days.

On account of the indefiniteness of the symptoms of iodoform poisoning great importance attaches to any positive means of recognizing the nature of the illness. Burlureaux affirms that if a piece of silver be placed in the mouth of a person suffering from iodoform intoxication, the taste of garlic will be immediately perceived, and that if some of the saliva be mixed with calomel, a canary-yellow precipitate of mercurous iodide will be obtained; according to Sasse, if a pinch of powdered calomel be placed upon a saucer, and a few drops of the urine from a case of iodoform poisoning be mixed with it by means of a glass rod, the yellow color will appear (yellow iodide). These tests prove only that the patient is under the influence of some compound of iodine, but, if correct, must in many cases be sufficient for the purposes of the practitioner.

After death from iodoform a very wide-spread fatty degeneration is to be found. This change appears to commence in the liver and rapidly to involve all tissues of the body. Floucaud states that there is a very distinct alteration of the blood-corpuscles.

The quantity required to take life is uncertain, but is probably between one and two drachms.

Therapeutic Uses.—Iodoform has been used internally, to a certain extent, in the same class of cases in which the inorganic iodides are employed. Although it is evidently capable of acting as an iodide, since a portion of it is decomposed in the stomach, it has no sufficient advantage to justify its internal use.

On the other hand, as a local remedy it has continuously maintained its place in the face of numerous substitutes and the obvious drawback of its powerful odor. Its greatest use has been as a dusting powder on infected wounds. While the clinical evidence is convincing that iodoform lessens suppuration and hastens healing, we cannot satisfactorily explain its mode of action. Two theories have been offered—one that it is decomposed by the secretions of the wound with the liberation of free iodine or some other powerful germicide, and the

second is that, absorbing the secretions, it keeps the wound dry and thereby discourages bacterial growth. Neither of these theories, however, can be considered satisfactory, for other iodine-containing powders which liberate iodine as freely as iodoform and which are as actively desiccant that have been suggested as substitutes for iodoform have not achieved the same practical success.

Iodoform has also been largely used by surgeons in the treatment of tuberculosis, especially of the joints. For this purpose a five to ten per cent. solution in olive oil is injected into the diseased area. The value of the drug in this condition, however, is less firmly established than as a dusting powder.

Iodoform has also an important field of usefulness as a local anæsthetic. It is not impossible that its value as a dusting powder in painful ulcers such as those following burns is due largely to the relief from pain. Its use as an anæsthetic around the nose and throat is greatly curtailed by its penetrating odor, but many surgeons rank it highly in the treatment of tuberculous laryngitis. The most important use of iodoform as a local anæsthetic is in various rectal conditions, as painful hemorrhoids and fissure *in ano*. In these conditions the official ointment may be used, or it may be employed in the form of suppositories containing from five to ten grains of iodoform combined with oil of theobroma.

Toxicology.—The symptoms of iodoform poisoning have already been sufficiently described. It should be pointed out, however, that the prognosis is always very grave, and the surgeon should, therefore, exercise peculiar caution in its avoidance. It must be remembered that the danger is in proportion to the area of wound surface over which the powder is spread. In small ulcers the absorbing surface is hardly sufficient to take up enough of the drug to do any harm, but in large wounds, such as are seen after burns, the danger is serious. Under no conditions should a surgeon ever apply more than one-half a drachm of iodoform to a wound.

Treatment.—Whenever any suspicious symptoms arise during the use of iodoform, the dressing should immediately be removed and the part well washed with warm water. The assertion by Sampter and Retzlaff that the potassium bromide is a chemical antidote by virtue of its dissolving iodine compounds has, so far as I know, received no clinical or experimental confirmation. There appears to be no other treatment of iodoform poisoning than the free use of water in the hope of aiding in the elimination of the iodine compounds to meet symptoms as they arise.

When applied locally to mucous membranes iodine exercises a powerful anæsthetic influence. It is not germicidal and its antiseptic influence is comparatively feeble. There is a wide-spread belief among surgeons that it has some special destructive effect upon tubercle bacillus, which is, however, not founded on any convincing experimental evidence.

Thymol Iodide.—Because of the disagreeable odor of iodoform a large number of iodine-containing compounds have been brought forward as substitutes. It cannot be said, however, that any of these have proven themselves clinically as the equal of the older remedy. Some of them, however, appear to have value, and the dithymol-di-iodide originally introduced under the trade name of aristol has been recognized by the United States Pharmacopœia. It is a light reddish-brown crystalline powder with a very faint odor, soluble in fats and in ether. It contains about 45 per cent. of iodine.

Thymol iodide appears to be almost non-toxic, although when introduced into the stomach it must be absorbed, since iodine can be discovered in the urine. It has been employed as a dusting powder for wounds and ulcers. Like iodoform, it has no direct germicidal power, but differs from iodoform in that it is much inferior in its local anæsthetic influence.

Bismuth Oxyiodogallate.—Under the trade name of airol there has been used for a combination of bismuth, iodine and gallic acid. This is a grayish, green powder which is readily decomposed by water with the liberation of iodine. It is used chiefly as a surgical dusting powder over ulcers, infected wounds and infections of the various mucous membranes. Its value depends upon the liberation of iodine by the secretions.

THYROID GLAND.

Under the name of *Thyroideum Siccum* the United States Pharmacopœia recognizes the dried thyroid bodies of the sheep. As it occurs commercially this is a yellowish powder with a somewhat meaty odor, and represents approximately five times its weight of the fresh thyroid gland.

Concerning the active principle of the thyroid gland there is much uncertainty. The only substance whose claims are at all worthy of consideration is iodothyrin, originally isolated from the gland by Baumann. A number of investigators have found that the injection of this substance will protect animals against the fatal results which ordinarily follow extirpation of the thyroid body, and Reid Hunt has shown that the activity of the thyroid body bears a relation to the percentage of iodine contained in it. On the other hand, the following facts would seem to call in question the claims of iodothyrin to be regarded as an active principle: first, the proportion of iodine in iodothyrin is not constant, so that it is hardly justifiable to regard this substance as a chemical individual; secondly, Hunt and Seidel have found that a large number of iodine-containing bodies are capable of producing the vital reaction which they had previously suggested as characteristic of the thyroid body, which result they attribute to a stimulation of thyroid secretion by these iodine compounds; and, finally, Asher and Flack failed to obtain the effects on the circulatory apparatus from iodothyrin which they obtained from the thyroid gland.

Physiological Action.—As is well known, the removal of the thyroid body in all mammals leads to serious disturbances of the bodily functions, and, if the removal has been complete, eventually death. The symptoms which have followed its removal in man are practically the same as those of the disease known as myxœdema: namely, increasing weakness with the deposit of a mucoid substance in the subcutaneous tissue, fall of body temperature, physical and mental deterioration, and finally a semi-comatose condition combined with gradual failure of all the vital functions.*

Circulation.—The intravenous injection of an extract of the thyroid gland produces but little obvious change in the circulation, although there is usually a slight fall in the blood-pressure and increase in the pulse-rate. The statement of Cyon that the thyroid gland increases the susceptibility of the vascular system to stimulation of the depressor nerve has been confirmed and extended by Asher and Flack. These investigators found that injection of thyroid substance or stimulation of the superior laryngeal nerve increased not only the fall of blood-pressure from depressor-nerve stimulation, but also the rise which follows the injection of adrenalin. It would seem, therefore, as if thyroid secretion increased the susceptibility of the vasomotor reflexes.

Thyroid feeding seems to have some influence, at present not clearly understood, upon the white corpuscles of the blood. Some investigators have found an increase in the number of these, but others, while not finding any change in the total number of leucocytes, have noted a relative increase in the proportion of mononuclear corpuscles.

Nutrition.—The most marked effects of thyroid feeding is upon the metabolic processes. It has been abundantly proven that either in the normal or the goitrous man or animal the administration of thyroid gland leads to a marked loss in the bodily weight, the rapidity of which is more or less proportional to the dose of the gland administered. Accompanying this loss of weight is a marked increase in the excretion of nitrogenous waste products over the intake of protein foods.

The loss of weight, however, cannot be explained solely, nor even chiefly, by the increased nitrogenous catabolism. It has been estimated by various authors that from one-sixth to one-third of the reduction in the bodily tissues is due to nitrogenous breakdown. The greater part of the loss of weight must, therefore, be looked for in the destruction of fatty tissues; indeed, Schöndorff believes that the destruction of nitrogenous tissue does not begin until after the excess of adipose is largely consumed. That there is an increased oxidation of the bodily fats has been directly proven by Magnus-Levy, who found an increase in the absorption of oxygen and in the exhalation of carbonic acid.

* In the earlier experiments upon the dog convulsive symptoms were described as characteristic of the removal of the thyroid. These convulsions, however, were due to the consentaneous removal of the parathyroids.

Besides this very manifest disturbance in metabolism, thyroid feeding influences other nutritive processes in ways which are at present not clearly understood. Thus its free administration will often produce a glycosuria which may persist for weeks after its withdrawal. In this connection may also be mentioned the interesting observations of Hunt and Seidel, who found that thyroid feeding increases the resistance of mice to poisoning by acetonitrile, but diminished the resistance of rats to the same poison and increased the susceptibility of both rats and mice to morphine.

Therapeutic Uses.—It is evident that a myxœdematous condition of the body is the result of the absence from the blood of some principle or principles which are supplied in the normal animals by the thyroid gland, and which may be furnished to the blood by feeding with thyroid glands. It is further apparent that the myxœdematous patient who has been relieved by such artificial supply must relapse when the supply is cut off; so that treatment of a myxœdema consists of two stages: first, that in which large amounts of the gland are administered in order to remove the results which have been produced by the lack of thyroid principle; second, the protracted stage of convalescence in which small doses of the gland are given continuously in order to prevent the recurrence of the myxœdemic symptoms. The most striking results are seen in cretinism or congenital myxœdema. In these a few months' treatment with thyroid gland may convert a misshapen imbecile into a well-formed child of normal intellect.

The destruction of fatty tissues under its use would seem to render the drug of great value in obesity. Unfortunately, however, the system soon becomes accustomed to it, and, although there is nearly always temporary benefit in properly-selected cases of obesity, the patients are very liable to relapse, even despite the continued use of the drug.

The diseases in which the thyroid body has been given include nearly all the chronic, and many of the acute, troubles known to humanity. In some of them it has seemed to be of benefit, but in most has proven useless. Among the conditions in which the thyroid has apparently proven of benefit clinically may be mentioned certain skin diseases, especially psoriasis and keloid, and certain uterine disturbances such as menorrhagia; it has also been recommended to hasten the union of fractured bones.

The condition known as exophthalmic goitre or Graves's disease is essentially one of hyperthyroidism, and can, therefore, only be aggravated by the administration of thyroid gland. The drug would seem to be also contra-indicated in diabetes mellitus.

Attention may be called to the experimental evidence of Hunt and Seidel that iodine increases the secretion of thyroid gland, which is in direct harmony with previous clinical experience.

Administration.—The thyroid gland may be given in the form

of the whole gland, either raw or slightly boiled, in the amount of one-quarter to one-half of a sheep's gland daily. This form of administration, however, has no advantage and is much more inconvenient than the official dried gland, which may be given either in capsules or compressed tablets. The beginning dose of the dried gland should be from one to three grains, increasing gradually until the evidence of beginning hyperthyroidism. The most characteristic symptoms of this condition are nervousness with fine tremors, rapid pulse, often with palpitation, and sometimes a mild degree of fever or insomnia. The occurrence of any of these symptoms should be the immediate signal for the withdrawal of the remedy. The dose of iodothyrin is about the same as that of the dried gland.

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THIOSINAMIN.

The name thiosinamin is applied to a carbamic derivative of mustard oil, allyl sulphocarbamide. This is a crystalline substance sparingly soluble in water but dissolves in solutions of sodium salicylate; fibrolysin is such a solution and represents 15 per cent. of thiosinamin. Of this solution 30 minims (2 C.c.) may be given at a dose.

Thiosinamin has been widely employed for the purpose of causing the absorption of various forms of fibroid tissue; thus it has been used for the relief of urethral and œsophageal stricture and sclerotic conditions of the middle ear, arthritis deformans, excessive scar formation and all other similar conditions. The clinical reports as to its usefulness have been more or less contradictory; some have recorded remarkable results while others have failed to obtain any benefit even after prolonged use. As regards the mode of action of thiosinamin we have no definite knowledge. By some its beneficial influence has been attributed to a leucocytosis, but the evidence that the drug produces any marked increase in the number of white blood-cells is not convincing, nor is there any explanation forthcoming of how a leucocytosis can break down organized fibroid tissue. The only rational theory explicative of its action which we have seen is that of Starkenstein. That author believes that he has shown that thiosinamin possesses the power of causing collagen to change into gelatin.

Thiosinamin may be administered by mouth, though better results are claimed for the hypodermic administration. For the latter purpose the solution known as fibrolysin is preferred; this is marketed in ampullæ, each of which contains sufficient for one dose. It may be injected every second or third day. For administration by the mouth from ½ to 1 grain of thiosinamin may be given two or three times a day.

In a number of instances the injection of thiosinamin has been followed by a characteristic system complex: chills followed by fever, sometimes as high as 104° to 105°, with headache, more or less prostration, sometimes nausea, vomiting, and occasionally disturbances of intellection.

PHENYLCINCHONIC ACID.

Phenylcinchonic acid, or atophan, occurs in the form of colorless crystals practically insoluble in water but readily soluble in alkaline solutions. It has a disagreeable, bitterish, somewhat glue-like taste. Under the name of novatophan has been introduced an ethyl ester of

methylatophan which is supposed to have the same effects upon the system as the older form of the drug, over which it has the advantage of being practically tasteless.

Physiological Action.—Atophan causes an increase in the elimination of uric acid which may amount to as much as 100 or even 200 per cent., without a corresponding increase in the output of the urea. In considering the practical application of this experimental observation certain facts must be borne in mind.

In the first place, the uric acid which is a normal constituent of the urine is derived in part from the metabolic processes of the body-cells and in part from the nucleo-proteids which are found in certain food stuffs, especially in the animal foods; the former being known as indogenous and the latter as exogenous uric acid. When a man is fed a weighed quantity of nucleinic acid, only about one-third of it appears in the urine in the form of uric acid or allied compound. While some believe that the reason for the appearance in the urine of relatively so small an amount of derivatives of the ingested nuclein is failure of absorption, the majority of those who have investigated the subject are inclined to the opinion that the major portion of the uric acid which is formed from the nuclein undergoes further oxidation and appears in the urine as some simpler nitrogenous compound, such as urea. Accepting this opinion, it is evident that a drug might increase the quantity of uric acid eliminated, by acting in one of three ways: (1) by increasing the rapidity of catabolism in those cells which are rich in nuclein; (2) by inhibiting the oxidating processes, thereby preventing the transformation of a portion of the uric acid into urea; or (3) by exciting either directly or indirectly the kidneys to more rapid excretion of uric acid which may already be present in the system.

Although several investigators believe that the increase in the amount of uric acid seen after the administration of atophan is due to a lowering of the oxidative processes of the body, thereby preventing so large a proportion of the uric acid being further metabolized, the larger number of authorities attribute the increased output of the purin bodies to an increased permeability of the kidney toward these substances. In favor of this latter view are the facts: that the increase of the uric acid occurs either on a mixed or a purin-free diet; that when uric acid is injected subcutaneously in the lower animals it is much more rapidly excreted under the influence of atophan than normally; and that the percentage of urates in the blood of gouty patients is diminished by the administration of the remedy.

Therapeutic Uses.—Atophan is used chiefly in the treatment of various forms of gout. Its value apparently is due not merely to the increased elimination of the purins but it also seems to possess more or less analgesic properties. By virtue of this latter action it is sometimes of service in neuralgia and arthralgia not of manifestly gouty origin.

The dose of atophan is from five to ten grains (0.3–0.6 Gm.) several times a day. It should be given with large amounts of water.

COLCHICUM.

Materia Medica.—*Colchicum autumnale,* or meadow saffron, is a small plant belonging to the lily family, found in Europe and England. The official portions are the seeds and the corm. The latter, which is often incorrectly called the root, is the thickened, swollen end of the stem with the little tuber attached, whose office it is to develop a new plant. This corm is solid and fleshy, an inch and a half to two and a half inches in length, with a longitudinal groove, having a nail-like process (the bulblet) at its base. In the shops it is very commonly kept in transverse slices, which are notched and cordate; the taste is bitter, hot, and acrid. Colchicum seeds are nearly round, about an eighth of an inch in diameter, and of a bitter, acrid taste. Colchicum depends for its activity upon the presence of an alkaloid *colchicine,* of which the seeds should contain 0.45 per cent. and the corm 0.35 per cent. Colchicine exists in the form of pale yellowish globules, or as an amorphous powder. It is soluble in 22 parts of water, freely soluble in alcohol and chloroform.

Official Preparations:

Fluidextractum Colchici Seminis.....2 to 6 minims (0.1–0.4 mil).
Tinctura Colchici Seminis (10 per cent.)....½ to 1 fluidrachm (2–4 mils).
Extractum Colchici Cormi.....½ to 2 grains (0.03–0.10 Gm.).
Colchicina .....$^1/_{100}$ to $^1/_{50}$ grain (0.6–1.3 milligm.).

Physiological Action.—The effects of a single dose of colchicum upon the lower animals do not appear to bear any relation to its therapeutic usefulness. Large doses do, however, exercise a marked action. According to Dixon and Malden, when colchicine is injected intravenously there is an immediate increase in the activity of unstriped muscle-tissue all over the body, with some slowing of the pulse and, after a period of several hours, a marked fall of the blood-pressure and diminution of respiration. The large dose also exercises a marked effect upon the bone-marrow, there being first a great fall in the number of polymorphonuclear corpuscles, with a consequent diminution of the total number of leucocytes, but twenty-four hours after the injection there occurs an enormous increase in the number of polymorphonuclear cells, the total number of leucocytes sometimes being doubled. At the same time there is an increase of nucleated red cells. That these changes of the blood are due to an effect upon the bone-marrow has been confirmed by the histological studies.

Our knowledge of the action of colchicum upon the metabolic processes is very unsatisfactory. There is much evidence that the output of uric acid, and often also of urea, is increased slightly. The present evidence points towards an increased catabolism rather than an increased elimination.

Therapeutics.—Colchicum is of no value in practical medicine

save in the treatment of gout, in which disease it has long been recognized as a specific. Our acquaintance with its physiological action is not sufficiently positive to establish any theory as to the method in which the drug acts. It may be that it simply increases the throwing off of gout-poisons, but this is not proved.

Colchicum may be used to prevent the coming on of a gouty paroxysm, or to lessen the severity of the symptoms when the paroxysm has already been developed. During an attack of gout, from fifteen to thirty drops of the wine of colchicum seed may be exhibited every four hours until some decided evidence of its action, such as nausea or slight purging, is induced. It should always be borne in mind that although looseness of the bowels may be useful, yet severe purging is to be avoided. In some cases, especially in debilitated subjects, the action of the drug upon the bowels should be restrained by the use of opium or other medicament. By large purgative doses of colchicum the paroxysms of gout may often be suppressed; but experience has shown that this use of colchicum is dangerous, the suppression being sometimes followed by serious internal disease, apparently due to a transfer of the gouty irritation. Between the paroxysms colchicum may steadily be exhibited to the gouty subject in small doses (twenty drops of the wine of the seed three times a day), and often great advantage is derived from its combination with potassium iodide. Ten grains of the iodide may be given with the colchicum wine three times a day.

In rheumatism colchicum has been highly recommended, but is of little value. Colchicum has been administered in various diseases, but when there is no rheumatic or gouty taint is at present very rarely used.

Toxicology.—In poisonous doses colchicum produces violent purging whose onset is soon followed by severe, often uncontrollable, vomiting. The discharges from the bowels are at first large and serous, but later become smaller, more mucous, with flaky deposits, and finally, in some cases, bloody. Abdominal pain may be absent or present, but if present is generally griping; sometimes there is gastric burning. Nervous symptoms have been prominent in some of the severe cases. Finally, a condition of collapse develops, the circulation fails more and more, the pulse, which has been frequent and feeble, becomes rapid and thready, the skin cold, pale, or livid, and bedewed with sweat, and death from exhaustion results. Consciousness is preserved until the last.

After death from colchicum the blood is generally found very dark and imperfectly coagulable, but whether this is due to a direct action of the poison or is the result of the slow death by asphyxia and exhaustion has not been determined. The chief changes are, however, in the alimentary canal, the mucous membrane of which is much swollen, intensely congested, sometimes ecchymotic, or with blood free in the intestine.

A striking peculiarity about colchicum poisoning is that in fatal cases the duration of life bears no relation to the size of the dose.

The *treatment* of colchicum poisoning is as follows: If the stomach and bowels have not been freely evacuated, administer at once an emetic and a cathartic, so as to empty the alimentary canal; allow the patient to drink freely of warm water, to aid in these operations and to act on the kidneys. Give freely of tannic acid, as the only known chemical antidote, although experiments upon animals have shown that it is not to be relied upon. To check the vomiting and purging, administer opium freely; and to allay the irritation, cause the patient to drink freely of albuminous matter, such as white of egg dissolved in water: the tannic acid having been given as soon as possible after the taking of the poison, the demulcents are useful in the more advanced stages. Symptoms of gastro-enteritis or of collapse are to be met as they arise.

THIOSINAMINE.

Clowe ..... J.A.M.A., 1911, lvi, 835.
Charteris ..... Glasgow Med. Journ., Sept., 1910.
Grossmann ..... Lancet, 1909, i, 157.
Starkenstein ..... Th. M., 1910, 68.
Walterhöfer ..... D.M.W., 1910, 1762.

ATOPHAN.

Folin and Lyman ..... J.P. Ex. T., 1913, iv, 539.
Frank ..... A.E.P.P., 1912, lxviii, 349.
Starkenstein ..... A.E.P.P., 1911, lxv, 177.
Weintrand ..... Ther. Geg., March, 1911.

COLCHICUM.

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Jackson and Blackfan ..... J.A.M.A., 1906, xlvii.
Patton ..... B.M.J., 1886, i.
Rossbach ..... Pharmak. Untersuch, ii.

GELATIN.

Gelatin is an albuminoid body obtained by boiling fibrous and cartilaginous tissues of animals. It is a purified form of the substance known as glue. It occurs in the market in transparent sheets, either colorless or with a slight yellowish tint, and generally bearing diamond-shaped marks left by the netting on which it was dried. Although insoluble, when immersed in cold water, it swells and softens and absorbs from five to ten times its weight of water. It is soluble in water in the presence of acetic acid and is freely soluble in boiling water. When its solution in hot water is allowed to cool it solidifies, forming a transparent jelly.

By prolonged boiling, or heating for shorter times to excessively high temperatures, or by the action of certain salts and ferments,

gelatin loses the property of solidifying when its hot solution is allowed to cool. Among other ferments which destroy this jellying power are the digestive ferments, which convert it into a substance called gelatose, analogous to the albumose formed by the digestion of proteins. Whether or not the loss of jellying power brought about by prolonged boiling is due to a conversion into gelatose is at present unknown.

Therapeutic Uses.—Aside from its pharmaceutical value—as for the formation of suppositories and the very convenient capsules—the sole claim which this substance has to inclusion in our materia medica rests upon its effect on the coagulation of the blood.

In 1896 Dastre and Floresco noted that when gelatin was injected into the vein of dogs the blood clotted with extraordinary rapidity. Shortly after this it was announced that the hypodermic injection of gelatin had the same effect in increasing the rapidity of coagulation. Although from time to time various experimenters have reported negative results from gelatin on coagulation time, yet the mass of both experimental and clinical evidence seems to be so overwhelming as to banish all doubt from the mind of the unprejudiced concerning the increase of the coagulability of the blood after the subcutaneous administration of gelatin. The question of whether the same effect follows the administration by the mouth cannot be positively answered. The substance, gelatose, which results from the digestion of gelatin, differs markedly in its physical properties from gelatin, and notably in that it does not jell. According to the author's experiments the peptic digestion of gelatin does not destroy its property of hastening coagulation of the blood. On the other hand, Ciuffini denies the efficacy of gelatose after prolonged boiling. There is, however, considerable clinical evidence that the oral administration of gelatin has a favorable influence in internal hemorrhage.

Although several theories of the mode of action of the gelatin have been suggested, none has been clearly established. The one which seems to the author to be the most reasonable, and the only one in favor of which there is any substantial experimental evidence, is that of Moll, who found that an increase in the fibrinogen content of the blood was caused by gelatin as well as certain other albuminoid bodies. The statement sometimes made that gelatin owes its clot-forming powers to its calcium content seems to me ridiculous.

Gelatin may be used clinically wherever it is desired to increase the coagulability of the blood. For instance, it is sometimes of service in the treatment of aneurisms. Its most frequent employment, however, is in the treatment of various hemorrhages, especially when from those areas which cannot be reached by local measures, as the lungs, or kidneys; it has, however, been used also as a local application to check bleeding, especially in gastric ulcers. It is employed often with good effect, although not always successful, in the treatment of blood dys-

crasias, as hæmophilia and purpura hæmorrhagica. It has also been employed for the purpose of increasing the coagulability of the blood in the treatment of aneurisms.

ADMINISTRATION.—The intravenous injection of gelatin is absolutely unjustifiable under any circumstances because of the very grave danger of the formation of thrombi. While there is little doubt that the hypodermic administration is more certain and more prompt than oral administration, the hypodermic use of commercial gelatin is not to be thought of, because of the grave danger of infection. The source from which gelatin is obtained makes it peculiarly liable to be contaminated with tetanus bacilli, and the spores of these micro-organisms are able to resist boiling temperatures for considerable periods of time. Simple boiling, therefore, will not assure the sterility of gelatin solutions, and a number of cases of fatal tetanus have followed the hypodermic injection of this drug. Under the name of *Gelatina sterilizate pro injectione,* Merck has marketed a ten per cent. solution which is manufactured from especially-selected material and sterilized by heating to a temperature of 115° C. Of this preparation from two to four ounces, representing 1½ to 3 drachms of gelatin, may be injected subcutaneously, preferably after previous dilution with hot physiological salt solution. If administered by mouth, from one-half an ounce to an ounce of gelatin, which may be exhibited in the form of a ten per cent. jelly, should be given three or four times a day.

COD-LIVER OIL.

Materia Medica.—Cod-liver oil is obtained from the liver of Gadus morrhua and of other allied species. In the manufacture of the so-called *shore oil,* the only variety employed in medicine, the fish caught near land are brought at once to the shore, and the oil is obtained by forcing steam at high pressure through a mass of the fresh livers enclosed in a metallic vessel, so as to tear them into pieces and melt out the oil. Cod-liver oil for medicinal purposes should always be perfectly limpid, yellow, free from rancidity, and have the peculiar taste and smell of the oil well developed. The cruder varieties, sometimes known as *straits* or *banks oil,* used in the preparation of leather and for other purposes in the arts, are prepared by allowing the livers to stand in casks and undergo putrefaction until the oil rises to the top, when it is skimmed off. The black or brown oil which results is extremely disgusting, both in odor and taste, and is loaded with the products of decomposition.

Cod-liver oil is a very complex substance, containing, besides fats and free fatty acids, cholesterol and various biliary principles, traces of iodine, bromine, phosphorus, and various basic amines, including trimethylamine, butylamine, and isoamylamine. Various authors have claimed to obtain from it various other basic substances, of which

aselline and morrhuine seem to be the most thoroughly established. The fats of cod-liver oil differ from most ordinary fatty substances in containing comparatively small amounts of the ordinary fatty acids, as oleic and stearic and palmitic; it is composed chiefly of glycerides of jecoleic and therapic acids. It was formerly taught that it contained an extraordinary amount of free fatty acids, but this is the case only in those varieties of oil which are made by putrefactive processes.

Official Preparations:

Oleum Morrhuæ .....1 to 4 fluidrachms (4–15 mils).
Emulsum Olei Morrhuæ (50 per cent.).....1 to 8 fluidrachms (4–30 mils).

Physiological Action.—Despite the assertions of manufacturers of certain proprietary extracts of cod-liver oil, there is no convincing evidence that any of the basic principles of cod-liver oil have anything to do with its therapeutic virtues. Its action is probably purely as a food. Its superiority as a nutrient in wasting diseases depends upon the ease of its absorption. It passes through animal membranes and through the coats of the intestines with a greater ease than any other known fatty substance, and is even capable of being absorbed through the skin in considerable quantities. To what this ease of absorption is attributable is at present uncertain, but it has been experimentally demonstrated to be true by a number of investigators.

Therapeutics.—Cod-liver oil is useful in medicine purely for its food value, but is a valuable remedy in many conditions of emaciation. It has been especially employed in various forms of tuberculosis, and if carefully administered can generally be given without disturbing digestion, and will add greatly to the caloric value of the food. The old superstition that cod-liver oil was a specific in consumption has been banished by the light of modern knowledge. It is useful also in various other conditions of malnutrition, such as rickets, certain types of chronic rheumatism, syphilitic cachexia, and, in fact, practically all conditions where the nutritive state is below par. It is not the disease but the general condition of the nutrition which should influence the practitioner in the employment of this remedy. Cod-liver oil is especially well borne by children, who rapidly acquire a great fondness for it. In adults, however, there is often considerable difficulty in the use of the cod-liver oil from the real or imagined inability of the patient to digest it. Without doubt, this very often arises from repulsion to its taste. The emulsions, because the taste is partially disguised, are generally more acceptable to the stomach; the addition of extract of malt to the emulsion of cod-liver oil affords one of the most palatable methods of exhibiting the oil. Often it is advisable to begin with a small daily dose and gradually increase the amount as the patient becomes habituated to its flavor. In young infants suffering with malnutrition cod-liver oil inunctions are often of service.

BENZOL.

The liquid commonly known as benzol is a mixture consisting chiefly of benzene, C_6H_6, and of toluene in varying proportions. A careful distinction must be made between benzene and benzin. The former is a definite chemical compound, the latter, which is often known for the purpose of distinction as petroleum benzin or as petroleum ether, is a mixture of the various more volatile hydrocarbons distilled from American petroleum. The two liquids are very different in both their chemical and physiological properties.

Although benzol has long been widely used in the arts, its employment as a remedial agent is comparatively recent. In 1912 Koranyi, because of the degenerative changes seen in the spleen and bone-marrow in benzol poisoning, experimented with it in leukæmia. The brilliant results which he achieved in this intractable disorder have been confirmed by a number of authors. Under its influence there is a marked diminution in the number of leucocytes and return of the spleen to normal size and restoration of weight and strength. How it acts is as yet uncertain. The observation of Schwartz and Steensland that it causes a lessening in the leucocytes in splenectomized as well as normal rabbits would seem to negative the view that its action is due to an effect upon the spleen. Whether the improvement which it brings about may be permanent or not, it is as yet too early to decide. Although there have been several relapses already reported, some patients have gone for a year or more without return of symptoms.

Benzol has also been employed, although to a lesser extent, in the treatment of Hodgkin's disease and polycythemia, and apparently has the same power for good in these conditions.

The dose is from 15 to 20 minims (1–1.3 mils) three times a day, mixed with an equal quantity of olive oil and enclosed in capsules.

The benzol treatment is not free from danger. Several fatalities have been reported from its use. After death severe degenerative changes have been found in the liver. During the administration of the drug it is important that daily blood-counts should be made.

GELATIN.

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Grau .....D.M.W., 1910, xxxvi, 127.
Moll .....W.K.W., 1903, xvi, 1215.
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BENZOL.

Koranyi .....B.K.W., 1912, 1357.
Meyers and Jenkins.....Albany Med. Annals, xxxiv, 381.
Muhlmann .....J.A.M.A., Nov. 29, 1913.
Schwartz and Steensland.....J. Med. Research, 1915, xxxiii.
Spiegler .....W.K.W., xxvii, 456.

CHAPTER VII.

DRUGS ACTING ON THE CAUSES OF DISEASE.

There are a number of agents of great value in practical medicine not so much because of any direct action upon the human body, but because of their effect on certain parasitic causes of disease. The latter may be divided into two groups—those belonging to the animal kingdom (protozoa) and those of the vegetable kingdom (bacteria). While most of the agents which are poisonous to one form of lower life are more or less so to all forms, generally, either because of some special toxic power towards some one organism or because of some concomitant circumstance, many of these agents are more or less narrowly limited in their field of usefulness to certain groups of animal or vegetable parasites; thus quinine has some antibacterial effect, but this is only feeble, while the plasmodium malariæ is extraordinarily susceptible, and the drug is little used as a general antiseptic. Again, corrosive sublimate is highly poisonous to intestinal parasites, but it is of no service as a vermifuge because of its toxicity to man.

The drugs which are used for their destructive action on the causes of disease may be divided into three groups: (1) Substances used to destroy intestinal parasites; (2) those used to combat protozoal infections, and (3) those used to antagonize bacteria.

ANTHELMINTICS.

These are medicines which kill or cause the expulsion of intestinal worms. It is obvious that the value of an anthelmintic depends not only upon its power of poisoning the articulate but also upon its harmlessness as regards the patient. Thus, it is the eminent combination of these qualities that renders the infusion of quassia so valuable in cases of seat-worms, while phenol, though very efficient, should never be used against the same parasite, since it has greatly imperilled, if it has not destroyed, the life of the patient when so employed.

Most of the drugs which are useful as vermifuges seem to depend for their action upon principles which are muscle poisons. Generally they do not completely kill the worm, but simply paralyze it, so that it may be carried out along with the other intestinal contents by violent peristalsis. For this reason the anthelmintic drugs should always be combined with or followed by an active cathartic. A considerable number of these principles are derivatives of phloroglucin.

There are certain general rules which govern the administration of anthelmintics, and which should not be lost sight of. They may be summed up as follows:

Let the alimentary canal be as empty as possible, so that the drug may act with the greatest force upon the enemy. For this reason

anthelmintics are best administered early in the morning; and in obstinate cases the patient should be required to fast until dinner time. If the drug be not itself a purgative, from four to eight hours after its administration a brisk cathartic should be given; or a purgative dose of calomel may be combined with it, as the bilious purging induced by the latter drug seems to be especially obnoxious to the entozoa.

ASPIDIUM.

Materia Medica.—*Filix-mas,* or *male fern,* is the rhizome of *Dryopteris filix-mas,* or male fern of Europe. Under the name of aspidium the present United States Pharmacopœia recognizes both it and the rhizome of the indigenous *D. marginalis.* The rhizome, when perfect, is from six to twelve inches long, and covered with large, brown, imbricated scales. Its taste is bitter and astringent.

The official oleoresin (Oleoresina Aspidii) thoroughly represents the crude drug. It is a dark, thick, liquid, of a bitter, nauseous, slightly acrid taste.

The therapeutic virtues of aspidium appear to depend upon a number of allied substances which were discovered by Boehm. The most important of these derivatives is filicic acid, which contains three methylated phloroglucin molecules in combination with butyric acid. Straub has shown that 0.01 per cent. of filicic acid is sufficient to paralyze nearly all invertebrate animals.

Physiological Action.—Filicic acid and the other principles of aspidium paralyze not only the contractile tissue of invertebrates, but they are also directly poisonous to the muscle substance of higher animals. In small quantities they appear to be somewhat stimulant to the central nervous system and produce, therefore, primarily increased reflexes and sometimes even tetanic convulsions, which is eventually followed by complete paralysis.

Ordinarily the oleoresin escapes absorption in the intestinal tract and passes out with the fæces, but in some cases, for reasons not known, it may be absorbed and, if it has been administered in large quantities, produce violent poisoning. The symptoms are excessive vomiting and purging, with general weakness, muscular tremors, and cramps in the extremities, exaggerated reflexes and in some cases tetanic convulsions, stupor deepening into coma, and collapse. A disturbance of the special senses is not an infrequent symptom, and permanent blindness has resulted from aspidium poisoning. Jaundice has also been noted, especially in prolonged cases, and appears to be due to a destruction of the red blood-cells.

Eight grammes (2 drachms) have proven fatal in a child of three years old, and six drachms have several times caused death in an adult.

Male fern is employed chiefly against the tape-worm. Ranozi reports favorable effects from its use in cysticercus; he gave eight grains (0.5 Gm.) several times a day.

PEPO.

Under this title the Pharmacopœia recognizes the dried seed of the pumpkin (*Cucurbita pepo*). These are oval, about three-fourths of an inch in length and an eighth of an inch wide, and of a pale yellow color. I. C. Wolff asserts that the active principle is a resin, but Power and Salway were unable to demonstrate any anthelmintic power either in the resin or the oil which they separated from the seed.

Despite the negative results of Power and Salway, the clinical evidence is so strong that one must concede that pepo is a valuable remedy in cases of tapeworm and has the great advantage of being harmless. Two ounces (60 Gm.) of the seeds previously deprived of their tegument may be administered, either in molasses or as an emulsion. Some hours after their administration a brisk purge should be given.

GRANATUM.

The bark of the stem and root of the pomegranate (*Punica granatum*), although very unpalatable, is efficient against the *tapeworm*. As originally stated by C. Tanret, pomegranate bark contains four alkaloids; the most important are *pelletierine* (*punicine*) and *iso-pelletierine* (*iso-punicine*). The official pelletierine tannate is a mixture of the four alkaloids.

Official Preparations:

Fluidextractum Granati .....30 minims (2 mils).
Pelletierinæ Tannas .....4 grains (0.25 Gm.).

In vertebrate animals pelletierine produces, in small doses, probably some stimulation of the spinal centers, but in any considerable quantity produces muscular weakness, and in sufficient dose complete paralysis. This paralysis is of peripheral origin, but whether the drug acts by paralyzing the peripheral ends of the motor nerves, like curara, or whether it is directly poisonous to the muscle substances, is as yet a matter of dispute.

SANTONICA.

Materia Medica.—Levant wormseed consists of the unexpanded flower-heads of *Artemisia pauciflora,* a composite of Northern Middle Europe and Asia. It consists of pale-greenish-brown, smooth heads of four or five tubular flowers of a very strong, aromatic odor when rubbed, and a bitter, disagreeable taste. The U. S. Pharmacopœia no longer recognizes the crude drug, the only official derivative being its active principle, santonin. This is the anhydride of santoninic acid, and occurs in colorless, pearly, four-sided, orthorhombic, insoluble crystals. It has a neutral reaction, but unites with alkalies to form salts, and hence is freely soluble in alkaline solutions. The dose is from 1 to 4 grains (0.06-0.25 Gm.).

As this drug is never used for its effects upon the human system, it is not necessary to enumerate in detail its physiological effects except to point out the two most characteristic results of large doses; namely, epileptiform convulsions, through a stimulant action upon the psychomotor area, and yellow vision (xanthopsia), which is probably due to a direct action upon the nervous elements in the retina.

Santonin is one of the most certain remedies that we possess for the destruction of the ascarides. Although it is not completely innocuous and cannot be used in unlimited quantities, in proper doses it is a reasonably safe drug. As absorption is to be avoided, the remedy is preferably administered in the form of coarse crystals, either enclosed in a capsule or made up into a lozenge, rather than in finely-powdered form. The soluble sodium santoninate should be strenuously avoided as a vermifuge.

Santonin has been used for various internal diseases, such as epilepsy, amenorrhœa, and amaurosis, but its value in these conditions is questionable.

Toxicology.—In poisoning by santonin great pallor of surface, with a blue color around the eyes or involving the whole countenance, has been generally an early symptom; vomiting has not rarely been present, and sometimes has been accompanied by colicky pains. Besides these manifestations, giddiness, mental apathy or stupor, great coldness of the surface, profuse sweating, trembling, mydriasis, and finally loss of consciousness, with convulsions and failure of respiration, are the usual phenomena of santonin poisoning. The circulation seems to be very little affected. The occurrence of xanthopsia is almost pathognomonic of the poisoning.

Usually this consists of a very deep yellow tint imparted to the landscape and to every object looked at—an effect comparable to that of looking through yellow glass. As was first pointed out by Knies, the period of yellow vision is usually preceded by one of violet vision, and during the stage of yellow vision, there is a lessening or complete destruction of the sensibility towards the violet end of the spectrum. Two theories have been advanced as to the cause of the yellow vision: first, that it is simply due to staining of the humors of the eye, and, second, that the disturbance of vision is due to the action of the drug upon the retinal elements themselves. The second theory seems to be the true explanation of the phenomenon.

The treatment of poisoning by santonin after free evacuation of the stomach and bowels is entirely symptomatic.

OIL OF CHENOPODIUM.

The *Chenopodium anthelminticum,* or Jerusalem oak, is a rank, odorous plant, growing about waste places in the suburbs in the United States. The seeds (sometimes known as American wormseed)

are minute, globular, light brown, and about the size of a pin's head, of a nauseous odor and a pungent taste, due to the volatile oil which they contain in large quantity.

The oil of chenopodium, the only derivative of the plant official (OLEUM CHENOPODII), is of a light yellow color, becoming darker and less fluid by age, of a peculiar powerful odor and a hot, burning taste.

The oil of chenopodium in large doses acts as a depressant to the spinal cord, the respiratory center, and the circulation. Added to the blood outside of the body it also causes methæmaglobin. According to the investigations of Brünning in the proportions of 1 part to 200 it has a distinct antiseptic action, while 1 to 5000 narcotizes but does not kill the *Ascaris mystax* (round worm of dogs).

The oil of chenopodium, although long neglected, appears to be one of the most efficient agents we possess, not only against the round worm but also against the tape- and hook-worms. Schuffner and Verwoort, in an elaborate comparative study of upwards of a thousand cases, found that the oil of chenopodium yielded a larger percentage of cures than either thymol or aspidium. Not only has the oil the advantages of certainty of action, but it appears to be one of the safest of the anthelmintics. Although there have been reported a number of cases of poisoning, some of which ended fatally, according to Levy in all of these cases the dose employed far exceeded that recommended by any authority for therapeutic purposes. The symptoms of poisoning generally do not appear until some hours after taking the drug, and consist of nausea, vomiting, ringing in the ears, often deafness, and, in the fatal cases, coma and convulsions.

The dose of oil of chenopodium against the round worm or tape-worm is from 5 to 10 minims (0.3 to 0.6 mil), but much larger quantities are required to destroy the hook-worm. It may be conveniently administered either by dropping it into a teaspoonful of sugar, following it by a dose of castor oil, or it may be directly dissolved in the castor oil.

SPIGELIA.

The rhizome and roots of *Spigelia marilandica,* or pinkroot, an herbaceous perennial, growing in the Southern and Southwestern United States. It consists of a knotty head, with numerous fine, crooked, branching rootlets. The odor is faint and peculiar; the taste sweetish and slightly bitter. W. L. Dudley separated from it an alkaloid, *spigeline,* which is asserted to be actively poisonous.

Physiological Action.—Full therapeutic doses of spigelia produce in man no symptoms, but an overdose causes acceleration of the pulse, dilatation of the pupils, heat and dryness of the skin, flushing and a swollen appearance of the face. According to H. A. Hare, toxic doses slow the pulse and depress the heart, the respiratory center, and the motor spinal cord.

Besides the vermifuges proper certain of the disinfectants, not-

ably thymol and betanaphthol, are clinically useful against intestinal parasites.

ANTHELMINTICS.

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Levy (Chenopodium) ..... J.A.M.A., 1914, lxiii, 1946.
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Power and Salway (Pepo) ..... Journ. Amer. Chem. Soc., 1910, 346.
Ranozi (Aspidium) ..... B.K.W., 1908, 2216.
Salant ..... A.J.P., 1915, xxxviii, xxxix.
Schuffner and Verwoort ..... M.M.W., 1913, lx, 129.
Schulz ..... J.A.M.A., 1911, lvii, 1102.
Straub ..... A.E.P.P., 1902, xlviii, 1.
Tanret (Granatum) ..... B.G.T., xcviii, 316.
Wolff (Pepo) ..... Monograph, Philadelphia, 1882.

ANTIMALARIALS.

CINCHONA.

Materia Medica.—The trees comprising the genus Cinchona, of which there are many species recognized by botanists, are handsome evergreens indigenous to South America, especially along the slopes of the Andes at an altitude of from five to ten thousand feet above the level of the sea. The United States Pharmacopœia recognizes the *Cinchona ledgeriana, Calisaya officinalis,* and—under the name of cinchona rubra—the *Cinchona succirubra,* as well as various hybrids of these species.

It is uncertain, but improbable, that the South African natives were acquainted with the medical properties of cinchona. The earliest record of its use appears to be in 1630, when Canizares, who was then governor of Loxa, one of the divisions of Peru, was cured of ague by its use. In 1638 the Countess of Cinchon, wife of the viceroy of Peru, was cured by the bark and sent a quantity of the remedy to Europe, where it was employed under the various names of "countess bark," "Peruvian bark," etc. In the early part of the last century it became evident that, owing to the reckless methods of collecting the bark, the natural source would soon be exhausted, and after various efforts to establish artificial plantations the Dutch finally succeeded, in 1853, in starting a successful cinchona grove in the island of Java. Since then the tree has also been successfully cultivated in India and Ceylon. Of the nearly eighteen million pounds of cinchona bark produced annually, over fifteen million pounds come from the island of Java, and about seven hundred thousand pounds from South America.

The official portion of the tree is the bark, which occurs in quills or curved bits of various size, externally of a grayish color, interior brown, and with a very bitter and somewhat astringent taste.

Although the cinchona bark contains a large number of alkaloids, only four are present in sufficient proportion to be of any practical importance. They are: *quinine, cinchonine, cinchonidine,* and *quinidine.* Of these the first three are official. The bark should contain not less than five per cent. of total alkaloids.

The alkaloid quinine occurs as odorless, extremely bitter, feathery crystals, soluble in 1750 parts of water but freely soluble in alcohol. Most of the neutral salts are but sparingly soluble. The sulphate—which represents 73.5 per cent. of alkaloid—requires 720 parts of water to dissolve it; the bisulphate dissolves in 8.5 parts, but contains only 59.2 per cent. of quinine. The neutral hydrochloride is dissolved in 18 parts of water, but the most soluble of the neutral salts is the double hydrochloride of quinine and urea, which is soluble in its own weight of water. The latter salt contains the same amount of quinine as the bisulphate. The hydrobromide dissolves in 40, the salicylate in 77 parts of water.

Official Preparations:

Fluidextractum Cinchonæ	15 to 30 minims (1–2 mils).
Tinctura Cinchonæ (20 per cent.)	1 to 2 fluidrachms (4–8 mils).
Tinctura Cinchonæ Composita (Huxham's Tincture) 10 per cent.	1 to 2 fluidrachms (4–8 mils).
Quinina	2 to 5 grains (0.13–0.3 Gm.).
Quininæ Sulphas	2 to 10 grains (0.13–0.6 Gm.).
Quininæ Bisulphas	2 to 10 grains (0.13–0.6 Gm.).
Quininæ et Ureæ Hydrochloridum	2 to 10 grains (0.13–0.6 Gm.).
Quininæ Hydrobromidum	2 to 10 grains (0.13–0.6 Gm.).
Quininæ Hydrochloridum	2 to 10 grains (0.13–0.6 Gm.).
Quininæ Salicylas	2 to 10 grains (0.13–0.6 Gm.).
Quininæ Tannas	2 to 10 grains (0.13–0.6 Gm.).
Cinchonidinæ Sulphas	3 to 15 grains (0.2–1.0 Gm.).
Cinchoninæ Sulphas	3 to 15 grains (0.2–1.0 Gm.).

Physiological Action.—Quinine is a protoplasmic poison and in sufficient doses capable of destroying the vitality of nearly all forms of unicellular life. It is, however, less poisonous to bacteria than to many forms of lower animal life. Among the organisms which are most susceptible to its action stands pre-eminently the plasmodia of malaria. Very small doses may increase the activity of the amœboid movements in these animalcula, but with sufficient dose this primary stimulation is followed by a decrease in activity and finally complete cessation and a granular degeneration of the organism. The parasite appears to be most susceptible to the action of the drug after the escape of the young sporular forms from the corpuscles in the blood. The gametes, as represented by the so-called crescent bodies of the *plasmodium falciparum,* are more highly resistant, and the fully developed crescents are not destroyed by ordinary doses of the drug, although their multiplication may be hindered.

General Action.—Locally quinine is irritant to mucous membrane. In sufficient concentration it has a powerful anæsthetic influence, coming on somewhat more slowly than after cocaine, but almost as complete.

Small doses are without any influence upon the blood-pressure, but large quantities, corresponding to 75 or 80 grains for a man, produce a marked fall of the blood-pressure, which is brought about by a depressant action directly upon the muscles of both heart and blood-vessels. In no dose is it stimulant to the circulation.

In the frog quinine produces a lessening of reflex activity, which diminution is abolished by destruction of the optic lobes and has, therefore, been believed to be due to an action upon the spinal inhibitory mechanism, the so-called Setschenow center. In dogs large doses produce restlessness, with muscular tremors and convulsions, followed by a loss of power, which deepens into more or less complete paralysis. The convulsions are probably of cerebral origin.

Tinnitus aurium is a familiar consequence of large doses of quinine. The fact that it is much more common in persons suffering from middle ear disease has led to the belief that it was due to disturbances of the circulation. This view has received some confirmation from the observation that after fatal doses marked congestion of the internal ear was observed, but Wittmaack has found distinct changes in the cells of the cochlear ganglion, and it is generally believed that the action of quinine upon the organs of hearing is directly upon the nervous mechanism involved. There is also an analogous effect upon the retina, although not so common, and disturbances of vision and even permanent blindness have followed from toxic quantities of the drug.

It has long been known that the application of considerable amounts of quinine, say one part to four thousand, arrests the movements of the white corpuscles and lessens their diapedesis through the walls of the capillaries, but this action probably plays no part in the therapeutic effects of the drug. According to Roth, it causes first a temporary increase in the lymphocytes, followed by a diminution below the normal, and later an increase in the polynuclear corpuscles and in the total number of white cells. Arkin asserts that it increases phagocytosis.

Small doses of quinine increase the vigor of the muscle contraction but apparently lessen its resistance to fatigue, and larger quantities greatly diminish muscle irritability. The application of strong solutions to the muscle produces a condition of rigor similar to that produced by caffeine.

Moderately large doses of quinine act as a stimulant to the uterine muscle, especially exaggerating the vigor of the normal contractions of the uterus and showing much less tendency to produce spasmodic contraction than does ergot. According to the researches of Cushny, this effect is due to a direct influence upon the muscle substance.

Metabolism.—Quinine produces a very marked lessening of the solid matters in the urine, chiefly of the nitrogenous products. The

lessening of the quantity of nitrogen excreted involves not only the urea and uric acid but the less completely oxidized forms of waste products, and since, after the withdrawal of the drug, there is no compensatory increase in the elimination of waste products, it is evident that this diminution is due not to any prevention of elimination, but is brought about through a lessening of the destructive metabolism in the proteid tissues. There is probably no substance used in medicine which so greatly reduces the nitrogenous metabolism as does quinine. The consumption of oxygen, however, and the output of carbonic acid do not appear to be correspondingly reduced.

Temperature.—Although in normal individuals, unless given in enormous quantities, quinine has no marked influence upon the bodily temperature, in febrile conditions it shows distinct antipyretic influence, and will even prevent the rise of temperature which ordinarily follows physical exertion. The fall of temperature in febrile conditions is usually accompanied with a decrease in both heat production and heat elimination. This fact shows, first, that the fall of temperature must be due to a lessening in heat production which coincides with the diminution in nitrogenous metabolism, and, further, the lessening of heat dissipation, which is secondary to the diminished formation, shows that the thermoregulator mechanism retains, at least in part, its normal function.

Absorption and Elimination.—Owing to the relative insolubility of basic quinine, it was formerly believed that the drug could be absorbed only from the stomach, but it has been shown by Grosser that even after the administration of large quantities of relatively insoluble salts only the merest traces of the alkaloid can be found in the fæces. It is, therefore, evident that absorption is complete and must be carried on in the intestines as well as in the stomach. The remarkable fact brought out in the research quoted is that, so far as the completeness of absorption is concerned, there was no demonstrable difference between the freely and the difficultly soluble salts; this, however, does not refer to the rapidity of absorption, but merely to the completeness of absorption.

After its absorption the alkaloid escapes from the system comparatively slowly. It appears in the urine in notable quantities, generally within a period of two or three hours, and from 20 to 50 per cent. of the quantity ingested is eliminated in the first twenty-four hours, but traces may be found in the urine as late as the third or fourth day. There is considerable evidence that some of the alkaloid is destroyed in the body, probably in the liver; from 75 to 80 per cent. of the amount administered is all that can be recovered unchanged. The other alkaloids found in cinchona bark differ, so far as known, from quinine merely in the degree of their effects. So far as the kind of action goes, they cannot be distinguished.

Toxicology.—The first symptoms of cinchonism, as produced by full therapeutic doses (ten grains) in man, are usually ringing in

the ears, slight fulness in the head, and perhaps some deafness. With the use of larger doses these symptoms are intensified: the deafness is very marked, disturbed vision may exist, and the flushed face, with a sense of distention in the head, may point towards a cerebral congestion, which is in some cases relieved by spontaneous epistaxis. In decided cinchonism, giddiness and staggering in walking are common. After toxic doses, severe headache, delirium, stupor, complete deafness and blindness, dilated pupils, embarrassment of respiration, great weakness, convulsions, paralysis, and finally collapse may result, either comatose or delirious. Quinine deafness usually passes off rapidly, but may be permanent.

More or less complete amblyopia may be produced by quinine and end in permanent loss of sight. In most of the numerous recorded cases the amount of quinine ingested has been very large, but in one individual twelve grains of quinine repeatedly produced temporary blindness. The disturbance of vision may come on abruptly or gradually. When fully developed it is usually accompanied by dilatation of the pupils, absence of the light reflex, and imperfect response to accommodative effort.

When the blindness is not complete there is usually pronounced contraction of the field, or, in rare cases, scotomata. The ophthalmoscopic examination commonly, but not always, has revealed pallor of the optic disks. The visual disturbances are due to a degeneration of the ganglion-cells of the retina and the optic nerves, which is by many attributed to a spasm of the retinal vessels.

Many persons show personal peculiarities or idiosyncrasy to quinine, and in these persons extraordinarily small doses may give rise to unpleasant or even dangerous consequences. The most common of these are various forms of dermatitis, which frequently closely resemble those of scarlatina. Occasionally marked circulatory depression has followed relatively small doses, and death has been reported from 0.5 gramme.

Therapeutic Uses.—The most important use for quinine is as an antiperiodic. Despite prolonged search and research, no substance has ever been discovered which can compare with quinine in the treatment of malarial fevers. Except in those rare conditions in which there are some contra-indications for the use of the drug, quinine is always the remedy of choice in all forms of plasmodial infection. Occasionally, however, cases will be found which, although resistant to quinine, may yield to other remedies. This is especially true in the case of the chronic forms of infection by Plasmodium falciparum, commonly known as æstivo-autumnal fever. (For the detailed use of quinine in malaria see page 343.)

Quinine has been used to a large extent as a curative agent in various infectious fevers, especially in septicæmia. It must be confessed that the scientific support for this use of the drug is very slender, but on the other hand there is a large amount of clinical testimony to its

favorable influence. It is evident from the study of its germicidal properties that it is impossible to introduce enough of the drug in the blood to directly affect the growth of the micro-organisms without endangering the life of the patient, but it is possible that it stimulates in some way the natural resistance of the body, either by increasing phagocytic activity or the formation of antitoxins. It is a familiar experience that many cases of acute coryza can be aborted by an early use of the drug, and several authors are positive of its value in pneumonia.

It is possible that at least part of the benefit which has followed its use is due to its antipyretic and anabolic actions. As an antipyretic, quinine, while less powerful than the phenol derivatives, is also less violent in its effects and, therefore, much safer. Theoretically, the fact that it acts by diminishing chemical changes in the body should also give it preference over the coal-tar substances, which increase, especially, heat dissipation. It is a useful remedy in typhoid and other fevers whenever a drug antipyretic is needed, especially when used in conjunction with hydrotherapeutic measures. The dose as an antipyretic should be from ten to twenty grains once or twice a day, which may be given per rectum if it proves irritant to the stomach.

Quinine, like other bitter substances, stimulates the digestive secretions, thereby improving the appetite and nutrition. It is probable, however, that in conditions of poor nutrition its effect in diminishing the breakdown of proteid tissues enhances its value as a tonic.

Conceiving the theory that choreic movements may be due to weakness of the spinal inhibition, H. C. Wood some years ago injected quinine into the veins of choreic dogs, and found that the movements were at once arrested by comparatively small doses of the alkaloidal salts. This led him to make trial of the remedy in the chorea of childhood, and as the result of much experience it has been determined that the drug in some cases of this affection is of great value. When there is no tolerance of quinine no benefit is achieved by its administration, but when the quinine is tolerated in large doses its use is commonly most beneficial. It has also proven of benefit in certain cases of nocturnal enuresis.

As an ecbolic quinine may be employed with good results in cases of delayed labor the result of uterine inertia. Although less efficient than ergot, it is a far safer remedy. For this purpose it may be given in doses of fifteen or twenty grains.

Recently the quinine and urea hydrochloride has come into considerable popularity as a local anæsthetic for minor surgical operations. It may be painted over mucous membranes or injected beneath the skin in strengths varying from one to ten per cent. It appears to act more slowly and less powerfully than cocaine, but is much less toxic.

Contra-indications.—On account of its irritant properties, quinine must be used with caution when there is irritability or inflammation of any part of the gastro-intestinal tract. It is strongly contra-indicated by inflammation of the middle ear, and may greatly and perma-

nently increase dulness of hearing. The statement of M. Friedmann that ergot, and that of W. B. Dewees that chloral, greatly lessens the tinnitus aurium produced by quinine and salicylic acid need confirmation. Irritability of the bladder or other portion of the genito-urinary tract contra-indicates the use of quinine: hence it is often badly borne by old men. Cases of hæmoglobinuria occurring during malarial infection have at times been attributed to the quinine, but the best authorities consider the irritation of the kidney to be due more to the disease than to the drug, and if the presence of parasites is demonstrated in the circulating blood occurrence of hæmaturia should not be regarded as a contra-indication of the use of the drug.

METHYLTHIONINE HYDROCHLORIDE.

Materia Medica.—Methylene blue, as this substance is commonly known, is the tetramethylthionine hydrochloride, and is prepared by the action of hydrogen sulphide upon the oxidation product of paramido-dimethyl-aniline. It is a dark-green, crystalline powder, with a bronze-like lustre, freely soluble in water with the formation of an intense blue color.

Medicinal methylene blue (Methylthioninæ hydrochloridum) has to be carefully distinguished from the dyestuff, which is a mixture of the chlorides of zinc and tetramethylthionine and contains various impurities, of which the most important is arsenic. When intended for internal use the drug must be free from arsenic and zinc. Parenski and Blatteis attributed the various unpleasant symptoms (nausea, vomiting, strangury, and the like) which have been reported to the confusion of the medicinal with the dye methylene blue.

Physiological Action.—We have but very little direct information concerning the effects of methylthionine upon the bodily functions. Clinical experience indicates that it acts similarly to the other derivatives of anilin, as would be supposed from its chemical structure. This conclusion is further confirmed by the fact that in large doses it causes methæmoglobin.

Elimination.—Methylthionine is absorbed rapidly from the intestinal tract and is eliminated chiefly through the urine, to which it imparts a greenish or blue color. Under certain conditions, however, the dye fails to color the urine, and it was at one time suggested as a test of the functional capacity of the kidneys.

It is probable, however, that the failure of coloration is due rather to the destruction of the substance in the body than to its retention. It also appears in lesser quantities in other secretions—for instance, in the saliva, to which it likewise imparts a bluish tint. When the drug is used therapeutically the patient should always be warned of the probability of this discoloration of the various excretions.

Therapeutic Uses.—The use of methylene blue in malaria was first suggested by Ehrlich and Guttman on account of the observation that it was possible to stain the plasmodia in the circulating blood. There

is much clinical evidence of its value in malarial fevers. Some years ago the author collected from literature and his own experience a series of 425 cases in which it was the sole drug employed, with 85 per cent. of recoveries. In ordinary acute tertian or quartan fever its effects are less dramatic than those of quinine, the disease ending with a gradual defervescence rather than the abruptness which is characteristically seen after the use of the cinchona alkaloids. It has been shown to exercise a direct destructive influence upon the plasmodium.

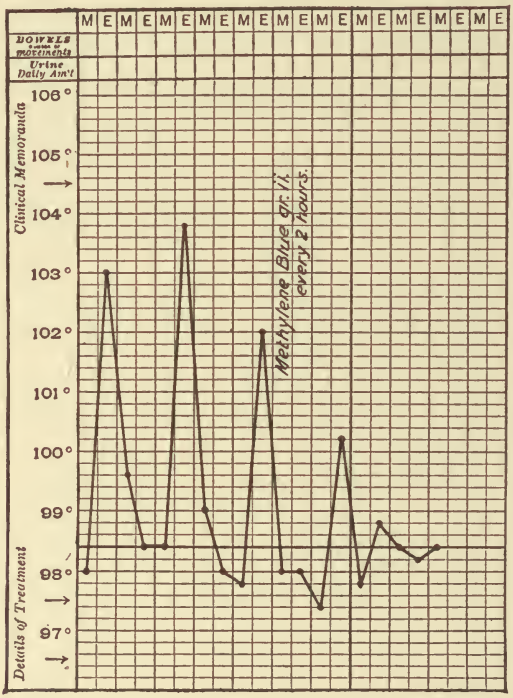

FIG. 27.—The effect of methylene blue in a case of tertian malaria. The continuous administration of two grains every three hours led to a rapid but not abrupt cessation of the paroxysms, with eventual complete cure.

Because of its lesser certainty and the comparative slowness of its action methylene blue is chiefly reserved for those cases in which there is some contra-indication to the use of quinine or in which the latter alkaloid has failed. It probably ranks second in efficiency as an antiperiodic.

Methylthionine has also been employed as a urinary antiseptic, especially in the treatment of gonorrhœa, but also in cystitis. The evidence of its value, however, in these conditions is not convincing. It was formerly used as an analgesic in neuralgic and rheumatic pains, and, although it has a distinct action in this direction, it is greatly

inferior to the ordinary coal-tar anodynes. In inoperable cancers it is asserted that it not only relieves the pain but also retards the growth of the tumor.

Administration.—In the treatment of malarial diseases with methylthionine it is necessary to continue the use of the drug for some time after the cessation of symptoms on account of the liability of relapse. From two to three grains (0.1–0.2 Gm.) may be given every three hours for ten days, and after this, three grains three times a day for a fortnight longer. In gonorrhœa the usual dose is two or three grains (0.1–0.2 Gm.) three times a day. The remedy may be conveniently given in pill form, but preferably enclosed in gelatin capsule to avoid the staining of the fingers and lips. The patient should always be warned of the probable discoloration of the urine.

EUCALYPTUS.

Materia Medica.—Of the Australian genus *Eucalyptus,** which comprises about one hundred and thirty-five species of evergreen trees, the United States Pharmacopœia recognizes only *E. globulus,* whose leaves are official, but allows the oil of eucalyptus to be distilled from fresh leaves of various species of the genus. From the various species of eucalyptus are prepared in Australia a number of volatile oils, and also the *eucalyptus gum* of the British Pharmacopœia. The so-called *red gum,* which occurs in commerce in kino-like grains or masses, contains nearly five per cent. of tannic acid, and is much used in making astringent lozenges.

Most of the eucalyptus oils are composed largely of either eucalyptol or phellandrene. The oils containing *phellandrene* were thrown out by the revisers of the United States Pharmacopœia, evidently under the impression that the active physiological portion of the oil is eucalyptol. Concerning the physiological action of phellandrene, however, we have no knowledge.

The oil of eucalyptus (United States Pharmacopœia) is a colorless or faintly yellow liquid, of a characteristic, somewhat camphoraceous odor and a spicy, disagreeable taste. It is generally considered to owe its activity to eucalyptol (cineol), of which it contains about fifty per cent. It is to be noted that the oil of cajuput contains the same active principle in and about the same proportion and is probably therefore therapeutically equivalent to the oil of eucalyptus.

The *oil of cajuput* is obtained from the leaves of *Melaleuca leucadendron,* a tree growing in the Molucca Islands. This volatile oil is of a green color, a peculiar fragrant odor, and a burning, camphoraceous taste.

* The *Eucalyptus globulus* is remarkable for combining extreme hardness of wood with a rapidity of growth asserted to be about five times that of our ordinary trees; it is also affirmed that shingles made of it are fire-proof. Its capability for absorbing and evaporating water is extraordinary, and to it has been attributed the freedom of Australia from malarial fevers.

The oil of cajuput should contain not less than 55 per cent. by volume of cineol (eucalyptol). The official preparations containing eucalyptol are:

Fluidextractum Eucalypti .....30 minims (2 mils).
Oleum Eucalypti .....5 to 15 minims (0.3–1.0 mil).
Oleum Cajuputi .....5 to 10 minims (0.3–0.6 mil).
Eucalyptol (Cineol) .....5 to 10 minims (0.3–0.6 mil).

Physiological Action.—Locally the oil of eucalyptus is decidedly irritant, causing a sensation of warmth in the mouth, fauces and stomach, with increased secretion. Its antiseptic properties are decided, but its action upon the lower infusoria is more powerful. In ordinary dose, so far as known, it has little influence on the general functions of the body, although it is asserted that it increases the nitrogenous elimination. In large quantities, however, it acts as a depressant to the motor side of the spinal cord and the medulla. The fall of blood-pressure which follows the administration of toxic quantities is due probably in part to a direct influence upon the heart, as well as its action upon the vasomotor center.

Eucalyptus appears to be eliminated through the kidneys, the skin, and the lungs, in which excretions its presence can be recognized by the odor. It sometimes imparts to the urine a violet-like odor.

Therapeutic Uses.—The oil of eucalyptus has some power as an antiperiodic, but is much inferior to the cinchona alkaloids and to methylene blue, and should be used only in cases in which for sufficient reasons these remedies cannot be employed, or as an adjuvant to them.

Oil of eucalyptus is one of the best stimulating expectorants that we possess: in both acute and chronic bronchitis it may be exhibited when there is free secretion. Children bear it very well. It is also a useful remedy against the ankylostoma and probably other intestinal parasites. It is also largely used locally as a stimulant antiseptic in various chronic inflammatory conditions of the mucous membranes of the upper respiratory tract.

The oil of cajuput has been used chiefly as an external parasiticide in various skin diseases, also as a local stimulant application in psoriasis, acne rosacea, and pityriasis. It is not very irritating to the skin, but is exceedingly destructive to low forms of life, and consequently has been used as a parasiticide externally, and even internally against the ascarides.

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THE TREATMENT OF MALARIA.

While in quinine we have a drug whose action in the malarial infections is as near specific as can well be hoped for, in order to accomplish the best results it is necessary that the drug be used in an intelligent manner, and the treatment of malarial fever is something more than the mere administration of the specific in indefinite quantities and at an indefinite period of the disease. The details of the treatment will differ according to the character and severity of the infection. We may consider first the treatment of the ordinary tertian or quartan fevers of moderate severity as commonly seen in temperate climes.

In the ordinary types of malarial infections seen in the northern parts of the United States the paroxysms of chills and fever usually recur at extraordinarily regular intervals, so that the patient can prophesy within an hour the period of the next paroxysm. It is a matter of importance to know this, because the paroxysm corresponds to the escape of the young sporules from the corpuscles into the blood stream, and it is at this stage of their existence that they are most susceptible to the action of the drug. It is, therefore, desirable that the maximum quantity of the drug shall be present in the blood at this time.

It is well to begin the treatment of these fevers, when of not dangerous severity, with the use of calomel purge, which at once cleanses the alimentary tract for the better absorption of the drug and

tends to relieve the hepatic congestion which is a common accompaniment of the infection.

There are two methods of administration of quinine, each of which is warmly advocated by competent authorities. In the one the physician places his trust in a single large dose of the remedy, hoping to destroy all the plasmodia in the blood at once, and in the other the beginning dose is somewhat smaller, but the remedy is continued, the idea of the treatment being that the first large dose will destroy the majority of the parasites and the continued use will kill those that remain as they reach the stage of development in which they are susceptible to the action of the drug. In this country at least the greater part of clinicians prefer the first of these methods. It may be carried out as follows: After having cleansed the intestinal tract with a mercurial purge, beginning six hours before the time of the expected chill the patient receives each hour from five to ten grains of one of the salts of quinine until from twenty to forty grains have been taken, the dose depending chiefly on the severity of the infection. This usually puts an abrupt end to the symptomatic manifestations of the infection, and no further quinine is administered for a period of six days. At the end of this time the course of cinchonization should be repeated, giving five grains every hour until twenty or thirty grains have been taken. In the interval between these times it is the author's custom to exhibit methylene blue in doses of 3 to 5 grains three times a day with the hope of exercising some deleterious influence on any plasmodia which may be left in the system. Some use arsenic for the same purpose. The advantage of giving quinine in broken doses is chiefly that there is less liability of an undesirable amount of irritation of the stomach.

The physician should always exhibit the alkaloid in some form which will insure its absorption. Because of its greater solubility the bisulphate is to be preferred among all of the official salts. It should never be administered in the form of pills, but either as a powder enclosed in gelatine capsules or in solution. The latter mode of exhibiting it has the advantage that absorption is more certain and that if freely diluted it is less likely to irritate the stomach, but has the great drawback of its extremely bitter taste.

When for any reason the quinine is contra-indicated, as with persons with middle ear disease or in those who are known to possess idiosyncrasy against the remedy, probably the next most reliable remedy is methylene blue. This is usually given in doses of two or three grains every second hour continuously for ten days to two weeks, without any reference to the time of paroxysm. It may be most conveniently exhibited enclosed in capsules.

In the æstivo-autumnal infections it is generally impossible to accurately prophesy the exact time of the next paroxysm, and it is, therefore, advisable in this infection to employ the continuous mode of exhibiting quinine. As it is this type of infection which is most

liable to become malignant in character, and as this may occur at any moment, no time should be lost in preparing the patient, but the use of quinine, in doses of about five grains every three hours, begun immediately and continued until the active manifestations of the disease have subsided, and after this five grains four times a day for a period of five or six days.

In the irregular types of malarial infections, the so-called dumb ague, the physician should first satisfy himself as to the etiology of the disease through examination of the blood, and if the parasites are found the treatment is carried out in the manner as for æstivo-autumnal infection.

In the so-called malignant or pernicious malaria it is essential that the patient be brought as rapidly as possible under the influence of the drug, and under these circumstances the intramuscular injection is preferable to administration by the mouth. For this purpose the bisulphate, being the most soluble, is the best of the official salts, although some unofficial salts are still more freely soluble. Among these the most popular are the bi-hydrochloride and the double hydrochloride of quinine and urea. The latter dissolves in less than its own weight of water and may be used for intramuscular injections in the proportions of one grain for each two minims of water. It is preferable to inject this deep into the muscle-tissue rather than subcutaneously, for the reasons that it insures more rapid absorption and also that there is less liability of subsequent local inflammations. The injections cause considerable pain, as the solution is locally irritant. The intravenous injection of quinine has been used with the happiest results by a number of authorities. For this purpose the bi-hydrochloride may be dissolved in physiological salt solution in proportions of about ten per cent. The same precautions are necessary, of course, in administering quinine intravenously as any other agent. The method is less painful than that of the intramuscular injection, and probably somewhat more efficient.

In pernicious malaria from ten to fifteen grains should be injected at once, either intramuscularly or intravenously, and this quantity repeated within four or five hours and followed by the exhibition of the drug by the mouth for several days. It is frequently necessary, in these severe types of infection, to support the strength with circulatory stimulants.

In cases of malarial hæmaturia, the so-called black water fever, a number of clinicians have recommended the avoidance of quinine because of its irritant effect upon the kidneys, but the disease is much more dangerous than the remedy, and nearly all the present authorities are unanimous that if the hæmaturia has been proven to be of malarial origin the drug should not be withheld.

As the result of malarial infections after the destruction of the parasites there is generally a marked degree of anæmia, which should be combated with iron and arsenic in ascending doses.

DISINFECTANTS.

Disinfectants are agents which are used for the purpose of preventing the growth of bacteria. This may be accomplished in two ways —either by killing the germs (germicides) or by rendering the media unfavorable for the growth of the micro-organisms (antiseptics). All chemical germicides become, however, when in dilute solution, antiseptic, so that the natural division of these agents, as given above, does not serve well as a basis of a classification for systematic study. Disinfectants, aside from strong acids and alkalies, may be divided into:

I. *Metallic salts,* including the salts of mercury, silver, copper, zinc, and iron.

II. *Halogens,* including chlorine and the hypochlorites, iodine, bromine, and their various compounds.

III. *Oxidizing disinfectants,* including especially hydrogen dioxide and potassium permanganate.

IV. *Carbon compounds,* including carbolic acid, cresylic acid, creosote, salicylic acid, benzoic acid, thymol, menthol, alcohol, formaldehyde, the volatile oils and allied drugs.

V. *Miscellaneous,* including sulphurous acid, boric acid, hydrofluoric acid, and their salts.

METALLIC SALTS.

Nearly all of the heavy metals have more or less marked antibacterial properties. This is true even of the metals in the elemental state, in which condition they are practically insoluble. It has been shown, for instance, that quantities of copper so small that the presence of the metal cannot be recognized chemically are sufficient to distinctly retard the growth of bacteria. The soluble salts of some of the heavy metals are among our most powerful germicides, notably those of mercury, silver, and copper.

The relative germicidal powers of the salts of any heavy metal appear to be in proportion to their ionization; thus, for example, among the mercurial salts the bichloride dissociates to the largest extent and is the most powerful germicide, and the addition of sodium chloride to solutions of corrosive sublimate lessens equally the ionization of the salt and its antibacterial properties.

MERCURY.

All of the salts of mercury appear to have more or less germicidal properties. The most powerful of them are the bichloride and the biniodide. The bichloride of mercury has long been recognized as one of the most powerful germicides known.

Micrococci and bacilli in active growth without spores are killed by solutions of 1 in 20,000, while solutions of 1 in 1000 will destroy the spores of *B. anthracis* and *B. subtilis.* According to the

experiments of Koch, the spores of *B. anthracis* are absolutely incapable of germinating in a proteid solution if as little as 1 part of corrosive sublimate in 300,000 be present. Sternberg has confirmed the conclusions of Koch.

The germicidal power of corrosive sublimate is greatly reduced by the presence of albuminous materials; for instance, Behring has found that, whereas one part of this salt in a million will inhibit the growth of anthrax bacteria in gelatine, in blood-serum it requires one part in ten thousand; and, again, while one in one thousand will destroy the viability of anthrax spores after two hours' exposure, in the presence of albuminous fluids the same solution acts with certainty only after twenty-four hours' exposure.

The practical utility of corrosive sublimate as a germicide is greatly lessened by its chemical instability. It is precipitated by albuminous matters and, therefore, cannot remain in solution when brought in contact with the bodily tissues. On many metals the corrosive sublimate deposits metallic mercury, forming an amalgam, and it is not, therefore, suitable for the disinfection of surgical instruments.

Because of the rapidity and certainty of its action and of its relative cheapness, bichloride of mercury is widely used for the purpose of disinfecting various utensils and articles of furniture which are not likely to be injured by it and which are not contaminated with large amounts of organic matter. For this purpose it may be used in solution of one part to 1000 of water.

The addition to corrosive sublimate of certain salts or acids, especially ammonium chloride and tartaric acid, greatly retards its precipitation by albumin and therefore it is the custom, whenever this substance is used for surgical disinfection, to add an equal weight of one of these substances. This combination is very widely used by surgeons for cleansing the hands and site of operation. It may be used for this purpose in the strength of one part in 2000.

The use of corrosive sublimate for washing out internal cavities is not a practice to be encouraged. A number of serious and even fatal cases have followed its use as intra-uterine, and even vaginal, douches, and its chemical instability renders it improbable that much disinfectant action can be accomplished from it.

The *biniodide of mercury* has been asserted by some authors to be even more active as a germicide. According to the experiments of Burgess, a 1 to 5000 solution of the biniodide is equivalent in strength to a 1 to 2000 solution of the bichloride. Sternberg has found that a 1 to 20,000 solution of the biniodide is equivalent to 1 to 15,000 solution of the bichloride of mercury.

One reason why the mercuric iodide has not come into use as a germicide is the fact that it is almost insoluble in water. It may be readily dissolved, however, by the addition of potassium iodide or lithium iodide to the solution.

SILVER.

Materia Medica.—The U. S. Pharmacopœia recognizes two forms of the nitrate and the oxide of silver. Pure silver nitrate occurs in the form of colorless, transparent crystals which, in the presence of organic matter, become gray or blackish on exposure to light. It has an astringent, metallic taste and is soluble in less than its own weight of water or in 24 parts of alcohol. The silver nitrate stick, commonly known as lunar caustic, which is also official, is made by melting silver nitrate in the presence of small amounts of hydrochloric acid and pouring into moulds. It occurs in the form of brittle sticks about the diameter of a goose-quill, grayish and semi-translucent. Silver oxide is a heavy, dark-brown powder, almost insoluble in water or alcohol. It is readily reduced by exposure to light, and with strong reducing agents yields up its oxygen so vigorously as to form explosive compounds. It is but little used as a medicine.

Incompatibilities.—Silver nitrate is one of the most unstable salts in the Pharmacopœia. It is precipitated by all the chlorides, iodides, bromides, sulphates, by albumin, by tannic acid, by carbonates and hydroxides and is reduced by light in the presence of even very small amounts of organic matter. The range of incompatibilities of silver nitrate is so wide that the physician should make it a rule to combine it with nothing but distilled water unless he is sure of the results.

Official Preparations:

Argenti Nitras .....¼ grain (0.015 Gm.).
Argenti Nitras Fusus.....External use only.
Argenti Oxidum .....1 grain (0.06 Gm.).

Physiological Action.—*Local Effects.*—In dilute solution silver nitrate produces that superficial coagulation of tissue which has already been described as the typical effect of the astringents. It differs from many other astringents, however, that in concentrated solution it penetrates somewhat more deeply and may act as a caustic, but its escharotic action is limited by the insolubility of the coagulum formed, so that it is not available where a deeply-penetrating caustic is desired.

The salts of silver rank next after those of mercury in their germicidal power. Although silver nitrate is distinctly inferior to corrosive sublimate in the absence of organic matters, in the presence of blood-serum it is apparently superior, for Behring has found that under such conditions a solution containing but one part of silver nitrate to 12,000 is sufficient to destroy anthrax spores if the exposure be sufficiently long (seventy hours).

According to Boer, a 1 to 4000 solution destroys typhoid bacillus in two hours (in the absence of albuminous substances), but it required a 1 to 2500 solution to kill the diphtheria bacillus in the same time. Behring found that a 1 to 10,000 solution is capable of destroying the anthrax spores in forty-eight hours.

Absorption and Elimination.—It is evident that in the stomach silver nitrate cannot long maintain its integrity. Bogolowsky has found that when the nitrate is added to a peptone it is readily dissolved, and that the solution formed does not coagulate albumin. That in this or in some other analogous form silver is absorbed is proved by its having been found in various internal organs and by the discoloration which follows its protracted use, known as argyria. When it is exhibited for a long continuous period, the skin often acquires a peculiar bluish slate color, which may become very dark, and in decided cases the conjunctiva and even the mucous membrane of the mouth are involved. The silver is found in all the tissues of the skin below the *rete Malpighii,* as well as in the kidney and various internal organs.

General Effects.—Although silver is occasionally still used as an "alterative," it has, so far as known, no direct physiological action which is of therapeutic interest. Most of the salts of silver cannot exist in the blood because of their affinity for albumin. When a non-precipitable salt of silver is introduced into the blood stream in large quantities it gives rise to very marked toxic symptoms, consisting of convulsions, followed by paralysis, which is due to an action apparently upon the spinal cord, with pulmonary œdema and respiratory embarrassment. After death congestion and ecchymoses are found in the lungs and other mucous membranes.

Therapeutics.—Silver was at one time employed as an alterative in various chronic conditions of the central nervous system, especially epilepsy and locomotor ataxia. The evidence as to its value in these conditions, however, is very uncertain, and its use has almost entirely gone out of vogue.

As local remedies certain salts of silver are of great importance. Of the official salts the only one which is used is the nitrate. This is used for three purposes: first, as an astringent; second, as a germicide, and, third, as caustic.

As an astringent silver nitrate is used in various inflammatory conditions of the mucous membranes, as in pharyngitis, laryngitis, urethritis, colitis, etc. It is quentionable how much of its value in these cases depends on its astringent effect and how much on its germicidal powers. In subacute pharyngitis it may be applied by means of a swab in strengths of ten to twenty grains to the ounce; in applying it the inflamed surface should be distinctly touched and not the whole throat daubed or slopped over with a large brush. In acute tonsillitis much benefit is often derived by painting the whole tonsil with a strong solution of silver nitrate, say forty grains to the ounce. The application of these strong solutions of silver nitrate is not as painful as one might imagine; the strong solution of silver nitrate appears to have some local anæsthetic action, which is probably dependent on its rapid caustic effect.

In cases of mucous colitis much benefit may be derived from the

high injection of dilute solutions of silver nitrate, especially if there are ulcerations. In this mode of treatment, the colon should first be washed out with an injection of plain water and then a quart of distilled water containing eight to ten grains of silver nitrate should be slowly injected, the hips of the patient being elevated to favor its flow into the upper part of the colon. If the enema is not returned within ten or fifteen minutes it should be followed by an injection of strong solution of sodium chloride in order to prevent the possibility of enough silver being absorbed to give rise to toxic symptoms. This treatment may be repeated every day or two as necessary.

In case of conjunctivitis, especially of gonorrhœal origin, dilute solutions of silver nitrate are of great value. In this condition it is generally applied in the strength of about two or three grains to the ounce. In acute urethritis silver nitrate is of great value, but should be used much more dilute in order to avoid the harmful effects from local irritation; appropriate concentrations would be from one part in 10,000 to one in 1000. Even these very dilute solutions have a distinct antiseptic and even germicidal power. In more concentrated solution it is useful as a prophylactic after exposure to gonorrhœa but the effort to abort an attack after the appearance of symptoms is of doubtful expediency, since when it fails it greatly aggravates the trouble.

Although theoretical objections have been raised against any possible value of silver nitrate in inflammatory conditions of the stomach, the clinical evidence of its value in subacute gastritis, and especially in gastric ulcer, is too strong to be denied. In order to obtain results from it in these conditions, however, it must be properly employed. It is essential that the drug be given on an empty stomach and that the internal lining of the stomach be cleaned of mucus, otherwise the silver nitrate will be unable to come in contact with the inflamed mucous membrane. The removal of the mucus may be accomplished either by means of lavage, or, if for any reason this is objectionable, a tumblerful of a warm solution containing from fifteen to twenty grains of sodium bicarbonate may be exhibited about fifteen minutes before the silver nitrate. The latter should always be administered in pill form, because the solution of silver nitrate is so unstable that it can hardly reach the inflamed area without decomposition; the precipitation of a solution will begin in the mouth by the chlorides and albuminous matters present in the salivary and mucous secretions, will be continued by the mucus lining the œsophagus, and what silver nitrate reaches the stomach unprecipitated will be immediately thrown down by the hydrochloric acid.

As a caustic silver nitrate, while superficial in its action, is quite powerful. It may be applied in the form of a concentrated solution, or more frequently by means of the stick of fused silver nitrate, to exuberant granulations and other forms of unhealthy ulcers. Its value in this condition depends not only upon its destroying the unhealthy tissue but also on its marked germicidal properties. In aphthous

stomatitis touching of the ulcers with the lunar caustic will usually start immediate healing.

Toxicology.—The symptoms produced by the ingestion of large doses of silver nitrate are partly gastro-intestinal and partly cerebro-spinal. In some instances the one series of phenomena predominate, in others those of the other class.

Vertigo, coma, convulsions, great muscular weakness, and paralysis, with intense disturbance of respiration, are in these cases the manifestations of disturbed innervation, while the abdominal symptoms are those of gastro-enteritis. The diagnosis can generally be made by the discolorations of the lips and skin—at first white, afterwards black—and by the blackish or brownish vomit; when the customary antidote has been given, both vomit and stools are generally white and curdy. After death the stomach and bowels are found corroded, often ecchymosed and with patches of a white or grayish color. Poisoning by silver nitrate is not common.

The treatment consists in the administration at once of large amounts of *common salt,* alkaline carbonates, or soap—the chemical antidotes—the constant use of large draughts of milk, and the meeting of symptoms as they arise.

Chronic *argyria,* or discoloration of the skin by silver, is usually unaccompanied by disturbances of health, although in severe cases the discoloration affects not only the skin, lips, gums, and sclera, but even the internal organs, such as the liver, spleen, and kidneys. It is therefore not due, as has been thought, to the silver chloride, since the latter becomes dark only under the influence of the light, but to a deposition of silver itself or of its oxide.

The removal of these areas of discoloration is chiefly a matter of time. Rogers states that blistering will lighten the color very much, and some authorities have claimed beneficial results from prolonged use of potassium iodide, but in many instances the discoloration of the skin persists for years despite the utmost efforts of the physician.

UNOFFICIAL SILVER SALTS.

In the effort to overcome the local irritant action of silver, which, it must be confessed, interferes greatly with its clinical usefulness, especially in gonorrhœal infections of the mucous membranes, a number of various compounds or salts of silver have been introduced. While many of these compounds are very much less irritant than silver nitrate, most of them are also less powerful as germicides, and it is doubtful whether their germicidal power is any greater in proportion to their local irritant effect than in the case of silver nitrate. Indeed, one of the most widely used of them, argyrol, has been demonstrated repeatedly to possess almost no germicidal powers.

The statement that silver compounds are germicidal in proportion to the amount of silver contained in them is certainly incorrect. For instance, according to Post and Nicoll 0.02 per cent. of silver nitrate

is more powerful than a ten per cent. solution of protargol, and Kelly states that silver nitrate is 250 times as powerful as protargol, while it contains less than nine times as much silver. It is more probable that the relative activity of the silver salts is in proportion to the amount of ionizable silver.

Although it seems to be pretty clearly shown that in solutions which are equally irritant to the mucous membrane of the eye the inorganic salts of silver are more powerful than the protein compounds, objection has been raised against the application of this fact to clinical medicine on the ground that the albuminous salts of silver not coagulating albumin retain their germicidal power in the presence of bodily secretions, and will be able, therefore, to penetrate into the crypts where the bacteria may be hidden. Concerning this theory of the value of the silver salts we have not sufficient data to draw positive conclusions, but Derby has shown that the presence of serum interferes with the germicidal properties of protargol and all these proprietary silver preparations, and, so far as their penetrating powers are concerned, both Kelly and Marshall and Neave found that the penetration of silver nitrate into agar-agar jelly was not greatly inferior to the silver proteins.

Considering all factors, it would seem doubtful whether any antibacterial influence in inflammations of the mucous membrane can be expected from any preparation of silver which cannot be obtained with equally slight disturbance of the vital reparative processes from nitrate of silver. Kelly, in a considerable series of cases of various types of infectious conjunctivitis, in which one eye was treated by irrigating either with physiological salt solution or boric acid solution and the other eye was treated with a silver compound, found that neither protargol nor argyrol shortened the duration of the disease. Many experienced ophthalmologists have believed, however, that they can obtain beneficial results from the cleansing or astringent properties of some of these salts of silver.

Silver citrate, which is sold under the trade name of itrol, is an almost insoluble white powder containing about 60 per cent. of silver. It is used either as a dusting powder or in the form of an aqueous solution containing 1 part in from 4000 to 8000 of water.

Silver lactate, or actol, is soluble in 15 parts of water, contains 51.5 per cent. of silver. While readily decomposed when applied to mucous membranes, it is claimed that it forms soluble compounds which are capable of penetrating the tissues.

Silver gelatose (*albargin*) is a yellowish powder readily soluble in water, containing about 14 per cent. of silver. It precipitates albumin, but very slowly. It has been used in one to two per cent. solution.

Argyrol.—This protein salt of silver, which is spoken of by the manufacturers as silver vitellin, occurs in the form of black microscopic scales containing about 30 per cent. of silver. It is freely soluble in water and not precipitated by either chlorides or albumin. According to Marshall and Neave, a 10 per cent. solution of argyrol kills the

pyogenic staphylococci in twenty-three hours' exposure, while one-tenth of one per cent. of silver nitrate destroyed them in five minutes. Post and Nicoll find that a 50 per cent. solution of argyrol is distinctly inferior in germicidal powers to a 1 to 10,000 of silver nitrate. Both Derby and Kelly have also found that even in 50 per cent. solution it is almost without any germicidal activity.

Largin.—This compound of silver and albumin is a whitish-gray powder, soluble to about 10 per cent. in water, freely soluble in blood-serum, not precipitated by albumin, and containing 11.1 per cent. of silver. It has great penetrating power when brought in contact with tissue, and has been highly praised by a number of German clinicians as a germicide in the treatment of gonorrhœa, both in men and women. It is used in strengths of one-fourth to four or five per cent.

Protargol is a freely soluble compound of silver and albumin, representing about 8 per cent. of metallic silver. Its solution is not affected by albumin nor hydrochloric acid. There has been much divergence of statement concerning its germicidal value. In the experiments of Derby a three or four per cent. solution was almost equivalent to a ½ per cent. solution of silver nitrate. Kelly finds that silver nitrate is 270 times as powerful as protargol. Post and Nicoll found that a 10 per cent. solution of protargol was approximately equivalent to a 1 to 5000 solution of silver nitrate.

Silver iodide is an insoluble yellow powder which was at one time recognized by the United States Pharmacopœia. Recently it has been employed in the form of a suspension in the treatment of gonorrhœal urethritis.

Ichthargan is a combination of silver with ichthyol, freely soluble in water, which appears to equal, if not surpass, nitrate of silver in germicidal influence.

SILVER.

Bogolowsky .....V.A.P.A., 1869, xlvi, 413.
Crede .....A.K.C., 1897, lv; also 1903, lxix.
Falk .....T.M., 1896, x.
Kelley .....B.M.J., 1907, ii, 1475.
Marshall and Neave.....B.M.J., 1906, ii, 359.
Rouget .....A. de P., 1873, 356.
Rozsahegzi .....A.E.P.P., ix, 295.
Wood, Jr. .....N.Y.M.J., April, 1903.

HALOGENS.

CHLORINE.

Chlorine is a yellow gas, extremely irritant to all mucous membranes with which it may come in contact.

Chlorinated Lime, or Bleaching-powder (often incorrectly called chloride of lime), is a grayish-white substance occurring in powder or friable lumps, having a hot, acrid, astringent taste, and an odor re-

sembling that of chlorine. It is made by the action of chlorine upon calcium hydrate, or slaked lime, and should contain at least thirty per cent. of available chlorine. It probably varies in its chemical constitution, but, according to the most recent views, is chiefly composed of the calcium hypochlorite and chloride. When exposed to the air it slowly evolves hypochlorous acid, which, being an unstable compound, undergoes spontaneous decomposition, and finally sets free fourteen-fifteenths of its chlorine. When an acid is added to chlorinated lime, the chlorine gas is rapidly evolved. If a specimen of bleaching-powder be very moist, it generally contains an over-proportion of the deliquescent calcium chloride, is correspondingly unable to liberate chlorine, and is therefore of inferior value.

Solution of Chlorinated Soda (Labarraque's solution) is made by triturating chlorinated lime with a solution of sodium carbonate. It is a greenish-yellow liquid, having a slight odor of chlorine and a sharp saline taste. It contains, among other substances, sodium hypochlorite, and possesses the therapeutic and disinfectant properties of the chlorinated compounds.

Compound Solution of Chlorine is made by adding hydrochloric acid to a solution of potassium chlorate, and should contain 0.4 per cent. of chlorine with some chlorine peroxide.

Official Preparations:

Calx Chlorinata [Bleaching Powder].....Not used internally.
Liquor Sodæ Chlorinatæ [Labarraque's Solution] .....½ to 2 fluidrachms (2–8 mils).

Germicidal Action.—When chlorine is brought in contact with moisture it unites with the hydrogen of the water, liberating nascent oxygen, which rapidly oxidizes organic substances. To this oxidizing effect are owing the bleaching qualities of the various preparations of chlorine. The affinity of chlorine for hydrogen is further manifest by the abstraction of this element from sulphuretted hydrogen; because of this action chlorine is deodorizant.

Chlorine, with the possible exception of the salts of mercury, is the most powerful chemical germicide used. Pure chlorine vapors in the absence of moisture are almost without germicidal action, but, according to Geppert, 0.03 per cent. solution of chlorine will kill anthrax spores in two minutes. Bolton found that a 1 to 2000 solution of chlorinated lime (representing 0.015 per cent. of chlorine) was sufficient to destroy typhoid bacilli after two hours' exposure, an effect which under the conditions of his experiment required a one per cent. solution of phenol; the anthrax spores were killed by a one per cent. solution (available chlorine 0.3 per cent.) in two hours. Niessen showed that a 0.5 per cent. to 1 per cent. solution could be relied on to destroy either typhoid bacilli or cholera spirilli in fæces within ten minutes. According to Duggan, a 2 per cent. solution of sodium hypochlorite,

representing 6 per cent. of available chlorine, will destroy anthrax spores in thirty minutes. This solution, however, is more than twice as strong as the official solution of chlorinated soda.

The solution of chlorinated soda is of little practical use except as a deodorizant. It should contain not less than 2.5 per cent. of available chlorine.

Therapeutic Uses.—As a means of disinfecting excreta chlorinated lime is without a rival. It has the great advantage over corrosive sublimate that its activity is not lessened by the presence of organic matters, and over phenol that it is not only much more efficient but much less expensive. In proportion to its germicidal power chlorinated lime is the cheapest disinfectant known. Besides its inexpensiveness and its certainty, it has the additional advantages that by virtue of its powerful oxidizing action it destroys the breeding places of germs as well as the micro-organisms themselves.

Chlorinated lime has been used successfully on a large scale for the purpose of disinfecting drinking water. Stokes and Hachtel found that from 0.5 to 1.5 per million of available chlorine has an efficiency of 90 per cent. For many purposes because of its oxidizing powers it is unsuitable; thus it bleaches nearly all colored woven goods and has an injurious effect on the more delicate fabrics. Internally chlorine today is used occasionally as an intestinal antiseptic in typhoid fever.

CHLORINE.

Duggan .....M. News, xlvi, 147.
Geppert .....B.K.W., 1890, No. 22.
Niessen .....Zeitschr. f. Hyg., viii, 62.
Sternberg .....Report National Board of Health, 1880.
Stokes and Hachtel..... .... ..J.A.M.A., li, 1505.

OXIDIZING AGENTS.

In this group are included a number of unstable substances which in the presence of organic matter yield up a portion of their oxygen. They differ in their oxidizing effect from chlorinated lime in that the oxygen is derived from their own molecule instead of from the air and, therefore, the amount of oxidation is limited by the quantity of the agent employed. It was formerly believed that the germicidal power of these substances was due to the nascent oxygen which they liberated, but it is probable that this is incorrect, and that the germicidal properties of these substances depend upon the action of the substance as a whole and not upon the oxygen they liberate.

In the presence of any reducing agent such as organic matter, these compounds yield up their oxygen very rapidly and lose their disinfectant value. For this reason, in the presence of large amounts of oxidizable organic matter, such as pus, their power to destroy bacteria is much less than when applied to isolated bacteria. This fact is the probable explanation of many of the discrepancies of statement concerning the

germicidal power of this group of agents. There are only two substances at present recognized by the United States Pharmacopœia which belong in this class; namely, potassium permanganate and the solution of hydrogen peroxide. Besides these, however, there are a number of substances containing in their molecule an excess of oxygen, which in aqueous solution unite with the elements of water to form hydrogen dioxide, and therefore have similar disinfectant properties. Of these, the U. S. Pharmacopœia recognizes sodium perborate.

POTASSIUM PERMANGANATE.

This salt occurs in slender, prismatic crystals of a dark purple color, inodorous, of a sweetish, disagreeable taste, and forming with water a solution varying from a purplish-black to a beautiful wine color, according to the strength. When kept dry, and not exposed to the atmosphere, potassium permanganate is a permanent salt, but whenever in solution it is brought into contact with an organic body it at once gives up its oxygen to the latter.

In the absence of organic matter potassium permanganate is probably a more active germicide than phenol. It appears to be especially poisonous to pus cocci, Sternberg having found that a 0.12 per cent. solution is sufficient to kill these organisms in two hours and equivalent to 0.8 per cent. solution of phenol. According to Koch, the anthrax spores are not destroyed by a one per cent. solution in two days, but a five per cent. solution is effectual in one day.

Incompatibilities.—Potassium permanganate is incompatible with nearly all metallic salts, with the alkaloids and all reducing agents, including nearly all the organic drugs.

Therapeutic Uses.—Potassium permanganate is used as a disinfectant wash for ulcers, abscess cavities, and purulent catarrhs, as leucorrhœa, ozæna, etc. To obtain any powerful germicidal effect in the ordinary methods of application requires a four or five per cent. solution. It is, however, frequently employed in very dilute solutions, ranging from 1 part to 1000 to 1 to 4000, for the purpose of washing out internal cavities, as the bladder. It is doubtful, however, whether these dilute solutions have any direct disinfectant property. Their value more likely depends upon their cleansing and stimulant influence on mucous membranes.

Potassium permanganate is also of service as an antidote to a number of poisons. Its injection in the immediate neighborhood of snake bites is generally conceded to be one of the most effective treatments, through oxidation of the venom. It also is capable of destroying many alkaloids, acting rapidly upon cocaine and morphine, but more slowly on strychnine. It is perhaps unnecessary to point out that this destructive action is purely local and the hypodermic injection of potassium permanganate in alkaloidal poisonings is a futile procedure.

The staining qualities of potassium permanganate greatly interfere with its use as a practical germicide. Kelly originated a method of

disinfecting the hands of the surgeon which has been adopted by a number of operators. It consists in soaking the hands and arms, after a thorough scrubbing, in a saturated solution of potassium permanganate until they are stained a deep mahogany brown, and then in a saturated solution of oxalic acid until completely decolorized, and rinsing in sterile water.

HYDROGEN DIOXIDE.

The official solution of hydrogen dioxide (*Aqua hydrogenii dioxidi*) is a colorless, odorless, slightly acid, aqueous solution of hydrogen dioxide (H_2O_2) containing, when freshly prepared, about three per cent., by weight, of the pure dioxide (corresponding to about ten volumes of available oxygen); a small amount of free acid is usually left in it as a preservative. It is apt to undergo decomposition, and should be kept in a cold place, and not too tightly stoppered, particularly in hot weather, lest there should be such a brisk evolution of oxygen in a confined space as to cause an explosion. Hydrogen dioxide has been employed to a considerable extent in the arts for bleaching and cleansing human hair, engravings, very fine textile fabrics, etc.

Hydrogen peroxide is an active coagulant of albumin, and when applied to bleeding surfaces acts as a styptic. In the presence of pus it effervesces actively, due to the liberation of gaseous oxygen; this reaction is sometimes used as a means of determining the presence of pus in deep-seated cavities, but if employed the surgeon should be assured of a free vent, otherwise the distention of the cavity by the gas may do much harm.

In the absence of organic matter the solution of hydrogen dioxide is an active germicide. Gifford found that 15 per cent. by volume (about 4 per cent. by weight) of hydrogen dioxide destroyed the anthrax spores in five minutes. This solution, it will be noted, is stronger than the official solution. A solution containing one per cent. of hydrogen peroxide will destroy many non-sporulating bacteria, if the exposure is sufficiently prolonged.

Therapeutic Uses.—Because of its non-toxicity the solution of hydrogen dioxide is widely used as an antiseptic application to mucous membranes; thus it is of value in diphtheria and other forms of infectious sore throat, in which conditions it may be applied pure by means of a swab, or diluted with equal parts of water as a spray. In surgery its usefulness is rather as a cleansing agent than as an antibacterial. It is of service for the purpose of washing suppurating ulcers, cleansing out abscessed cavities and the like.

SODIUM PERBORATE.

Because of the rapidity of deterioration of hydrogen peroxide and for certain reasons of convenience, there have been introduced a number of salts which liberate their oxygen in the presence of water with the formation of hydrogen dioxide. These include the so-called peroxides, perchlorates, persulphates, and perborates. Of this group, the U. S. Pharmacopœia recognizes sodium perborate. This occurs as a white crystalline powder, permanent in dry air but yielding its excessive oxygen in a warm, moist atmosphere. In solution it undergoes chemical change with the formation of hydrogen dioxide and sodium metaborate as in the following formula: $NaBO_3 + H_2O = NaBO_2 + H_2O_2$. As the resulting solution is alkaline, there is a rapid decomposition of the hydrogen dioxide with the evolution of oxygen gas. The Pharmacopœia directs that sodium borate shall contain not less than 9 per cent. of available oxygen.

The rapidity with which the free oxygen is liberated from these salts depends largely upon the degree of alkalinity of the resulting compound; thus the sodium peroxide, which gives rise to the highly alkaline sodium hydroxide, causes a rapid decomposition of the hydrogen dioxide and consequently exercises more violent oxidative powers than does the sodium perborate.

If, as seems at present probable, the antibacterial properties of hydrogen peroxide depends not on the liberation of oxygen but on inherent properties of the whole molecule, then it is evident that, while solutions of sodium peroxide may be more powerful as bleaching agents, those of sodium perborate would be more active germicides. According to Herbol, a 2 per cent. solution of sodium perborate is equivalent in disinfecting powder to a 0.4 solution of hydrogen dioxide.

Sodium perborate is used as a disinfectant—either as a powder or in solution—to wounds and ulcers, as an antiseptic mouth-wash, and for various other purposes for which dioxide of hydrogen is used. According to Herzfeld, it is useful in epistaxis. Magnesium peroxide has been used in gastric conditions both for its disinfectant and antacid properties.

POTASSIUM PERMANGANATE.

Fodera ..... Archiv. di Farmacol. e Terapeut., 1901, xi, 239.
Kelly ..... Amer. Journ. Obstet., 1891, xxiv.
Rogers ..... Indian Med. Gaz., 1912.
Sternberg ..... M. News, Jan. 10, 1885.

HYDROGEN DIOXIDE.

Gifford ..... N.Y.M.R., 1888, 243.
Goodman ..... Penna. Med. J., 1910, 339.
Harris ..... T.G., 1902.
Marshall ..... U.P.M.B., 1902.

SODIUM PERBORATE.

Herbol ..... D.M.W., 1908, 1092.
Herzfeld ..... J.A.M.A., 1911, lvii, 1613.

CARBON COMPOUNDS.

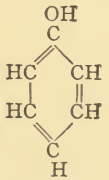
A large number of hydroxyl derivatives of the closed-chain series possess marked germicidal power. The most widely known of these compounds is phenol or carbolic acid. The term phenol is applied in chemistry in a generic sense to any derivative of benzol in which one or more of the hydrogen atoms is replaced by a hydroxyl, as well as, in a narrower meaning, to the simplest of the series. Most of these phenols have been shown to be possessed of antibacterial properties. Those which are sufficiently used to justify consideration are phenol, thymol, resorcinol, cresol, and guaiacol. Besides, these several acids belonging to the benzene series have also been used as antiseptics. The most important of these are benzoic acid, salicylic acid, and cinnamic acid.

When two benzene rings are united we have formed the substance naphthalene, popularly known as tar-camphor. Bearing a relation to this substance similar to that which the phenols do to benzene are the substances known as naphthols. The only one which is used to any extent is the betanaphthol, which is a very powerful germicide.

Besides these disinfectants from the closed-chain series in this chapter will be considered also one belonging to the open-chain compounds —namely, formic aldehyde.

PHENOL.

Phenol (carbolic acid, phenylic alcohol, hydroxybenzene) is a substance obtained from coal-tar by distilling at a temperature of between 300° and 400° F., adding to the distillate a hot concentrated solution of potassium hydroxide, and, after this, water, separating the light oily matters which rise to the top, and adding hydrochloric acid to the heavy alkaline bottom layer, when impure carbolic acid separates. This impure carbolic acid is of a dark color, and contains several congeneric bodies, especially xylic and cresylic acids. These acids are as active germicides as is phenol, so that crude carbolic acid is very largely used.



Phenol.

When pure, phenol forms, at ordinary temperatures, colorless, transparent plates or long, rhomboidal needles, but as ordinarily seen is pinkish or red in color. In dilute solution it has a sweetish, somewhat tar-like taste, and produces a sensation of numbness in the mouth. When exposed to the air it absorbs moisture and liquefies, forming an oily-looking fluid. The official phenol should contain not less than 96

per cent. of absolute phenol. The addition of water equivalent to 8 per cent. of the weight of the phenol forms with it a clear liquid. On further addition of water, however, the solution becomes cloudy until about twenty times the weight of the phenol has been added, when a clear solution is again formed.

Phenol is faintly acid to litmus and unites with caustic alkalies, forming compounds known as phenolates. These unions, however, are so feeble that they are decomposed even by carbonic acid.

Although soluble in water only to the extent of five parts in one hundred, it is very freely soluble in alcohol, glycerin, and oils.

Official Preparations:

Phenol [Carbolic Acid].....1 to 2 grains (0.06–0.13 Gm.).
Phenol Liquefactum (86.4 per cent.).....1 to 2 minims (0.06–0.13 Gm.).
Glyceritum Phenolis (16 per cent.).....5 to 10 minims (0.3–0.6 mil).
Unguentum Phenolis (3 per cent.) [Carbolated Vaseline].....External use.

Physiological Action.—In concentrated form carbolic acid is a mild escharotic, its momentary application to the sound skin producing burning pain and a white discoloration which changes to a reddish stain, gradually fading away as the skin desquamates. If the application be prolonged an eschar forms.

The dilute solution of phenol is locally anæsthetic not only to mucous membranes but even when applied to the skin.

Phenol, even in relatively dilute low concentrations, precipitates albumins from solution. The coagulum formed is not hard and firm, like that produced by the metallic salts or tannin; it is not unlikely that it is due rather to changes in the solvent than to chemical union with the protein, for the phenol can be washed out from the precipitate and the albumin is then found unaltered. Its action is analogous in this regard to the precipitation of globulins by alcohol. Because of the fact that it does not enter into chemical combination with the albumins its antibacterial activity is not destroyed, as is the case, for example, with corrosive sublimate, although its penetration may be interfered with.

Phenol is one of the oldest and one of the most popular of germicides, but its power and reliability are usually much overestimated. While a one per cent. solution will destroy nearly all non-sporulating bacteria in a few minutes at ordinary temperatures, a 5 per cent. solution is not certainly fatal to anthrax spores even after twenty-four hours' exposure. As an antiseptic it requires a solution of 1 in 850 to certainly prevent the multiplication of bacteria. Its antibacterial effect is much enhanced by warmth and by the addition of acids, notably hydrochloric acid.

General Effects.—In frogs phenol in large doses produces tremors of the muscles, followed by marked convulsions with exaggerated reflexes, both of these symptoms probably being due to effects upon

the anterior horns of the spinal cord, followed later by paralysis. In the lower mammals these symptoms are also seen, but the convulsions are less permanent than the tremors, and in man are generally altogether lacking.

In the early stages of phenol poisoning both the respiration and pulse-rate are increased in frequency, and become later slower than normal. The cause of these changes is not definitely known, but they are probably due to actions upon the nervous mechanism regulating these functions. There is seen, after large doses of phenol, marked fall in the blood-pressure, which is due primarily to paralysis of the vasomotor apparatus, although the heart muscle probably shares in the depressant effect. These changes in the circulation are caused only by toxic quantities.

Phenol, like its derivatives, the coal-tar anodynes, has an influence in lessening the bodily temperature. It differs from these in that it acts not only in febrile conditions but also in normal animals, and that it is much more prone to produce collapse.

Elimination.—Phenol, after its absorption, escapes from the system comparatively rapidly, chiefly through the kidneys, partially as oxidation products—especially the dioxy-benzenes, pyrocatechin and hydroquinone—but chiefly in combination with glycuronic and sulphuric acids. The smoky color of the urine which is seen after large doses of phenol is due to the oxidation compounds which are formed.

Therapeutic Uses.—In doses in which it is usually given phenol has no effect upon the general functions of the body, and it is doubtful whether it is of service in any internal diseases. It has, however, been employed with asserted benefit in certain infectious diseases, notably rheumatic fever and tetanus. It is perhaps unnecessary to point out that if it does any good in these conditions it certainly is not as an antiseptic, because in doses which can be borne by the human organism the dilution in the bodily fluids would be so extreme as to entirely preclude any possibility of an effect upon bacteria.

For its local anæsthetic action phenol is a very valuable remedy in the treatment of various forms of nervous irritability of the gastro-intestinal mucous membranes, especially when there is also a tendency to fermentative changes in the food, as the result of imperfect digestion. In nervous vomiting, and in gastrodynia, it may be given in doses of from one to two grains, repeated at intervals varying from fifteen minutes to two hours, according to the symptoms of the case. Also in various irritative conditions of the skin, such as urticaria and pruritus, it is a very valuable sedative, applied generally in a one or two per cent. solution.

The most important use of phenol, however, is as an antibacterial. On the subject of its surgical use it is unnecessary to dwell at this point, except to call attention to two important facts: First, that its local anæsthetic influence often enhances its value as a disinfectant to wounded surfaces, but, on the other hand, lessens its utility as a dis-

infectant for the surgeon's hands. The second important point is that the prolonged use of even dilute solutions of phenol in some way interferes with the nutrition of the part, and a number of cases of local gangrene have followed its application as a germicide. The deep injection of phenol in a 2 per cent. solution for the purpose of combating localized inflammations, such as phlegmons, is enthusiastically recommended by a number of surgeons.

As an antiseptic in the mouth and throat phenol is one of the most valuable remedies we possess. It has the advantage over the widely-used thymol and benzoic acid that it is much less irritant to mucous membranes in proportion to its germicidal power. Its flavor in dilute solution is not disagreeable, and can easily be effectually disguised by the aromatic oils. As a mouth wash or spray in various forms of infectious sore throat it may be used in one-half to one per cent. solution, preferably containing ten to twenty per cent. of glycerol.

As an intestinal antiseptic phenol, although widely used, is certainly inferior to many of its allies, because after diluted below the germicidal strength, which it must be rapidly by the intestinal contents, it very soon loses even its antiseptic power.

Toxicology.—Probably on account of the ease with which it is procured and the quickness of its action, phenol is among the most popular of poisons. According to Harris, out of five hundred and forty-nine fatal cases of poisoning with it which occurred in England during four years four hundred and twenty were suicidal.

The symptoms usually appear in a very short time after the ingestion of the poison, and when the dose has been sufficient may develop so rapidly that death occurs within three minutes. Usually the patient lives from one to ten hours, and life has been protracted for sixty hours.

Usually, but not always, a burning pain is first felt in the mouth, œsophagus, and stomach, followed in a few minutes by nausea, cold sweats, and stupor deepening rapidly into insensibility and collapse. During the period of insensibility, complete abolition of reflex movements and anæsthesia of the mucous membranes have sometimes been noted. Indeed, it is scarcely doubtful that in all cases both sensibility and reflex movements are profoundly affected. Convulsions are only exceptionally present. The symptoms of collapse are usually well developed, and the pulse is generally feeble and very frequent, but has been recorded as being slow, forty to fifty per minute. Respirations are usually rapid and dyspnœic in character and sometimes stertorous; later in the poisoning the breathing becomes slow and shallow, death occurring in the midst of a profound coma, the immediate cause being respiratory failure, although the circulation is also greatly enfeebled. The smallest quantity known to have taken life in the adult is a little over one drachm. Attention may be called to the fact that the free external use of carbolic acid is not without danger, even to life.

The diagnosis of phenol poisoning, even although the symptoms are so lacking in characteristic feature, should generally be comparatively easy. In the first place, the characteristic odor is easily found about the patient or on his breath; on the mucous membranes of the lips and mouth will generally be observed white hardened or corrugated patches due to the local action of the drug. Generally, also, the urine will be found to have a blackish or greenish color which is almost characteristic of poisoning by some member of the phenol series.

The urine as first passed is usually of a normal color, but upon standing in the air becomes greenish or smoky in color. Occasionally the characteristic discoloration of the urine is not seen, although the absence of phenol or its oxidation products may be regarded as proving that the case is not one of phenol poisoning.

The *postmortem* lesions of phenol poisoning are usually well marked. If the acid has been ingested in a concentrated form, white, hardened spots are found upon the mucous membrane of the mouth, œsophagus, stomach, and even intestines. They are, of course, due to the local action of the poison, and are sometimes blackish in the center, or even blackish throughout, and very generally are surrounded by a red inflammatory zone. The liver, spleen, kidneys, and indeed all the organs, are found filled with dark, imperfectly coagulated blood, such as is habitually found after death from asphyxia, and there is generally evidence of inflammatory changes in the kidney.

In the treatment of phenol poisoning the emetics are of little value, because of the paralysis of the sensory nerves of the stomach. The viscus should be emptied by means of the stomach-tube. As phenol is but sparingly soluble in water, the stomach should be washed out with dilute alcohol.

Alcohol is, however, in no proper sense antidotal to phenol. It simply acts as a solvent. The action of alcohol in removing the local effects of phenol is due simply to the fact that it washes away the poison. It is important to remember this in the treatment of internal poisoning by phenol, so as to avoid leaving any of the alcohol in the stomach, as this would aid in the absorption of the drug. After using alcohol the stomach should be washed out with water or salt solution in order to remove the last trace of alcohol.

As an antidote to phenol the most popular remedy is sulphuric acid or one of its salts. After absorption phenol combines with the sulphates of the body to form harmless compounds, and it was at one time generally believed that the same reaction would take place in the stomach with artificially introduced sulphuric acid. Recent investigation, however, has thrown grave doubt on the antidotal value of the sulphates, but as they do not do much harm they may be used in the absence of any more satisfactory antidote.

In the practical treatment of phenol poisoning the best that can be done after washing out the stomach with a ten per cent. solution of

alcohol or twenty per cent. solution of whiskey is to treat symptomatically, using demulcent remedies for the gastritis and stimulants as indicated.

PHENYL SALICYLATE.

This substance, commonly called salol, is a white, nearly tasteless, insoluble crystalline powder, which is prepared by replacing one atom of the hydrogen of salicylic acid by phenol. It is decomposed by alkalies, and, consequently, is broken up in the intestinal tract, yielding about thirty-six per cent. of phenol and sixty-four per cent. of salicylic acid. Although less powerful as a poison than are its united ingredients, probably because it is broken up slowly in the intestines and escapes with the fæces to some extent unchanged, salol is capable of producing concurrent symptoms of salicylic acid and of phenol poisoning.

Salol was originally introduced into medicine as an antirheumatic, but the proportion of phenol present is so much that to get sufficient salicylic acid to have a distinct influence upon the system requires a quantity so large as to introduce a serious danger of phenol poisoning. Although it is occasionally used in the milder forms of rheumatic pains, its most important use in medicine is as an intestinal antiseptic.

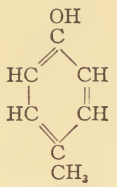
Phenyl salicylate of itself is a feeble antiseptic, but in the intestinal tract it is slowly decomposed with the liberation of phenol and salicylic acid, both of which are actively germicidal. It is used to a large extent as an intestinal antiseptic in acute enteritis, in intestinal fermentation, and similar conditions. It may be given in doses of from five to fifteen grains several times a day.

Phenol-Sulphonic Acid.—Both the sodium and zinc salts of *sulphocarbolic acid* are official in the United States Pharmacopœia (Sodii Phenolsulphonas, Zinci Phenolsulphonas). The sulphocarbolates were introduced some years ago as intestinal antiseptics, for which purpose it was evidently expected they would possess the antiseptic virtues of carbolic acid and the innocuousness of the sulphocarbolates. It has been shown, however, by Withers that they are not possessed of any direct antiseptic power. More recently it has been claimed for them that they are decomposed in the intestinal tract with the liberation of carbolic acid, but we know of no experimental or scientific evidence tending to show the truth of this belief, and their value is extremely doubtful.

CRESOL.

Under the name of Cresol is recognized by the United States Pharmacopœia a mixture of three isomeric oxytoluenes—the orthocresol, metacresol, and paracresol. The mixture occurs in commerce as a colorless or straw-colored refractive liquid with a phenol-like odor, soluble in sixty parts of water and miscible in all proportions with

alcohol and glycerine. It is a later product of the fractional distillation of coal-tar, and is practically the substance which has long been known in commerce as *cresylol,* or *cresylic acid.*



Paracresol.

Cresol is soluble in sixty parts of water at 25° C., but is rendered more soluble by the presence of soap. This is the explanation of the complete miscibility with water of the official compound solution of cresol, as well as the various proprietary preparations of cresol. The addition of lime salts and the use of hard water in making solutions of compound solution of cresol, on account of the insolubility of the lime soaps, produce a turbidity of the solution, which, however, it is claimed, does not interfere with its germicidal activity.

A large number of proprietary preparations of cresol are upon the market, mostly soapy solutions or emulsions. The most widely known of these are lysol (containing 50 per cent. of cresol) and creolin (containing 2.7 per cent.).

Official Preparations:

Cresol .....1 to 2 minims (0.06–0.12 mil).
Liquor Cresolis Compositus (50 per cent.).....External use.

The germicidal power of cresol is certainly much greater than that of phenol. Fox has found that one-half per cent. solution of the official Liquor cresolis compositus (which contains 50 per cent. cresol) destroys non-sporulating bacteria in from ten to fifteen minutes, as compared to fifteen to sixty minutes for same strength of phenol, and that the anthrax spores are killed by a solution containing 2.5 per cent. of cresol in forty-eight hours, as compared to a 5 per cent. solution of phenol, which required sixty hours. He concludes that the compound solution of cresol is about twice as powerful as pure phenol.

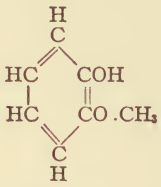
As regards the effects of cresol upon the human system comparatively little is known. Because of its relative insolubility it is generally less toxic than phenol, but, according to Blumenthal, there occur annually in Berlin one hundred cases of lysol poisoning, and Fries, out of twenty-seven cases of poisoning from the internal use of lysol, reported thirteen deaths, so that the statement that cresol is non-toxic is certainly incorrect. Symptoms which have been caused are very similar to those of phenol poisoning.

Cresol is a valuable substitute for phenol as a germicide for all

purposes for which the older preparation is used. In strengths of corresponding germicidal power it has the advantage over phenol of being less caustic and less poisonous. Because of its greater solubility the compound solution of cresol is nearly always employed. The saponaceous character of this preparation makes it of especial value for cleansing the skin. Although its extremely unpleasant taste and odor interfere with its use as an intestinal antiseptic, cresol has been used with benefit in diarrhœas and intestinal putrefaction in doses of one to two minims.

GUAIACOL.

Guaiacol is the monomethyl ether of pyrocatechin. It occurs as a colorless crystalline solid, and also as a syrupy liquid of an agreeable aromatic odor. It is soluble in fifty-three parts of water and very freely in alcohol and ether.



Guaiacol.

Guaiacol Carbonate (*Duotal*) occurs as a neutral, white, almost tasteless and odorless crystalline powder, insoluble in water, soluble in forty-eight parts of alcohol.

Official Preparations:

Guaiacol .....5 to 10 minims (0.3–0.6 mil).
Guaiacolis Carbonas .....10 to 20 grains (0.6–1.2 Gm.).

Guaiacol acts in concentrated form as an irritant and as a germicide. As originally pointed out by André, it has also distinct anæsthetic properties, which are not, however, sufficiently pronounced to make the drug useful as a local anæsthetic. In the experiments of J. Kuprianow guaiacol was found to be distinctly inferior to creosote and to phenol in general germicidal influence, but to be especially poisonous to the tubercle bacillus.

Guaiacol is absorbed both through mucous membranes and skin with great rapidity; it has been recognized in the urine fifteen minutes after its local application to the skin. It is eliminated chiefly in combination with sulphuric acid or glycuronic acid. The general physiological action of guaiacol has not been carefully studied, but appears to be similar to, although less powerful than, that of phenol. Its antipyretic action is apparently, however, superior to phenol.

Therapeutic Uses.—As a disinfectant guaiacol is comparatively little used externally, but has been used as a urinary antiseptic in

cystitis, especially of the tuberculous varieties. From fifteen to thirty minims of a five to twenty per cent. solution in sterilized olive oil may be injected daily into the bladder.

Guaiacol was at one time recommended as an antipyretic in the treatment of typhoid fever, pneumonia, and other acute infections. It was applied externally in the following manner: The skin of the abdomen or chest, after thorough cleansing, is painted, by means of a camel's-hair brush, with from twenty to fifty minims of the drug, and an impermeable dressing applied to prevent evaporation. While the fall of temperature followed with great certainty, it has too often been excessive and accompanied with pronounced collapse, so that as a practical antipyretic the drug has been almost completely abandoned.

The most important use of guaiacol is as a stimulant expectorant in chronic bronchitis, especially when associated with tuberculosis. It is generally employed, however, in the form of creosote. Inhalations of the aqueous solution (1–600) have been used in phthisis, but it is not probable that they have any effect except that of a stimulant one to the mucous membranes of the lungs.

Guaiacol carbonate is much used as a substitute for guaiacol on account of its freedom from taste and of its being less irritant to the stomach; it is apparently, however, less active either as a local or general remedy.

CREOSOTE.

Under the name of creosote the United States Pharmacopœia recognizes a colorless, oil-like liquid which is obtained by the distillation of wood-tar, preferably that derived from the beech (*Fagus silvatica* or *Fagus ferruginea*). It is a mixture of various phenol bodies, containing from sixty to ninety per cent. of guaiacol, besides carbolic acid, cresol, and xylenol, or dimethyl-phenol. Crude carbolic acid was at one time sold as coal-tar creosote, but the term creosote should be strictly limited to the substance obtained from wood-tar. It has a caustic taste and a penetrating odor suggesting that of phenol, and when pure is colorless, although frequently it occurs with a brownish tinge. Its solution in 140 parts of water is not perfectly clear, but it mixes in all proportions with alcohol and the oils.

Under the name creosotal is sold a mixture of the carbonates of the various constituents of creosote containing about 90 per cent. of creosote. This is a thick, oleaginous, pale-yellow, almost tasteless liquid, insoluble in water but soluble in fatty substances.

Official Preparations:

Creosotum .....5 to 15 minims (0.3–1 mil).
Aqua Creosoti (1 per cent.).....½ to 1 fluidrachm (2–4 mils).

Physiological Action.—The effects of creosote upon the system appear to be very similar to those produced by phenol, although it is less actively toxic. Locally it is, like phenol, paralyzant to the sensory

nerve-endings and, in sufficient concentration, destructive to all forms of protoplasm. The absorption from the intestinal tract and elimination are both rapid, about two-thirds of an ordinary dose escaping from the system within nine or ten hours after its administration. It is eliminated chiefly through the kidneys in combination with sulphuric and glycuronic acids, but is also partly eliminated through the lungs.

As a germicide creosote appears to be distinctly superior to phenol, especially so in dilute solution; a 0.3 per cent. solution will kill non-sporulating organisms in a few minutes. As an antiseptic, that is as an agent to inhibit the growth of bacteria rather than to destroy their viability, it ranks among the most powerful agents we possess, a solution containing one part in three thousand being sufficient, according to Guttmann, to completely inhibit the multiplication of all bacteria.

Therapeutic Uses.—Because of its relative insolubility creosote is but little used as a surgical disinfectant. As a gastro-intestinal antiseptic in cases of fermentative gastritis or enteritis it is one of the most valuable remedies we possess. It is also of service in various conditions of irritation of the mucous membrane of the stomach for its local antiseptic influence.

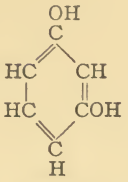
Externally creosote has been used as a germicide in various forms of skin diseases and as a local application in leucorrhœa, diphtheria, and other infectious conditions of mucous membranes. Probably through its precipitation of proteins it has a slight hæmostatic influence which sometimes is of service.

The most important use of creosote is as a stimulant expectorant in chronic bronchitis and in phthisis. It is by some believed that creosote in cases of phthisis is beneficial not merely as a local stimulant to the mucous membrane of the lungs but also because of its antiseptic action. The evidence, however, that creosote administered by the mouth exercises any distinct antibacterial influence in the lungs is far from conclusive.

The ordinary dose of creosote for internal use is five minims, but when well diluted so as to avoid irritation of the stomach much larger quantities can be administered, some enthusiasts using as high as one-half to one fluidrachm at a dose. In administering these large quantities it is necessary, to avoid irritation of the stomach, that they be freely diluted in the proportions of about two or three minims of creosote to the fluidounce of water.

RESORCINOL.

Resorcinol (*resorcin*), *pyrocatechin,* and *hydroquinone* are three dioxybenzols, resembling each other very closely in physiological effects, but of which only resorcinol is official. This occurs in short, colorless prisms or plates, becoming reddish when exposed to the air, with an unpleasantly sweet, somewhat acrid taste. It is soluble in half of its weight of water, also in alcohol or ether, and in about twenty parts of fixed oil.



Resorcinol.

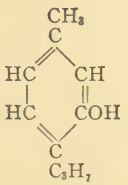
Physiological Action.—Resorcinol in concentrated solution is an active irritant, but is scarcely capable of exercising any caustic effect. It is eliminated in the urine chiefly in combination with sulphuric acid, and its excretion is said to be complete within seven hours. Its general influence is similar to that of phenol, although it is somewhat less active as a poison.

The antibacterial power of resorcinol appears to be much inferior to that of phenol.

Therapeutic Uses.—Although resorcinol has been used to some extent for its antiseptic action upon mucous membranes, as in gastritis, pharyngitis, urethritis, etc., it is far less valuable for this purpose than some of the other phenol bodies. Its most important use is in the treatment of various skin diseases, in which it appears to be valuable not merely through its antibacterial action, but also by virtue of its stimulant effect upon the skin. In active inflammatory conditions of the skin it should not be used stronger than one per cent. solution, but in chronic eczemas and various parasitic diseases, as scabies and tinea, it may be used in the strengths of three to five per cent., preferably in solution.

THYMOL.

Thymol is para-propyl-metacresol, and is found occurring naturally in a number of essential oils, notably that of the thyme (*Thymus vulgaris*). It forms colorless crystals practically insoluble in water but freely soluble in alcohol. It has a characteristic aromatic odor and a highly irritating aromatic taste.



Thymol.

It liquefies when triturated with equal parts of menthol.

Locally thymol is intensely irritant to mucous membranes, and in strong solution is mildly caustic. The statements concerning its germicidal powers are so divergent that it is difficult to draw definite conclusions. Thus de la Croix found that it required 1 per cent. solution

to destroy bacteria, while, on the other hand, Cooper finds that in the absence of organic matter it is 25 times as strong as phenol, although in the presence of organic matter its phenol coefficient is only 8. Its antiseptic strength is variously stated as from 1 in 1500 to 1 in 10,000.

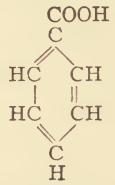
Because of its sparing solubility in water it has generally been believed that thymol is absorbed from the intestinal tract only to an insignificant extent, but the experiments of Seidell indicate that this belief is incorrect; some of the thymol appeared in the urine in combination with glycuronic acid, but the greater amount could be recovered neither from the fæces nor urine, so that it would seem that in some way it is destroyed in the body. As it is soluble in fats, it is generally recommended that oils be avoided when thymol is used.

Therapeutic Uses.—Because of its supposedly agreeable taste—although to the author phenol has a less objectionable flavor—thymol has been used very largely as an antiseptic in diseased conditions of the mouth and throat in strengths of from one to two parts in a thousand, solution being aided by the addition of a little alcohol. Its intense irritant action, however, greatly lessens its value for this purpose. It is also used as an intestinal antiseptic in doses of 2 to 5 grains (0.12 to 0.3 Gm.).

The most important present-day use of thymol is as a vermifuge, especially against the hook-worm (*Ankylostoma duodenalis*). For this purpose very large doses are required. Ten to 30 grains (0.6 to 2 Gm.) may be administered in capsules every hour for three doses, and followed with a saline purgative. If the intestines are not promptly cleaned out, toxic effects may be produced. The characteristic symptoms of thymol poisoning are ringing in the ears, free sweating, fall of bodily temperature, and frequently delirium. The urine is of a dark greenish color.

BENZOIC ACID.

Benzoic acid may be obtained by sublimation from gum benzoin but is to-day chiefly manufactured synthetically either from toluene or naphthalene. It occurs in white, feathery crystals of a silky lustre, with an acid, pungent taste, and, when pure, odorless; but that which is prepared from benzoin generally has a fragrant, vanilla-like odor, due to the presence of traces of a volatile oil. It is almost insoluble in water, but its ammonium and sodium salts are very freely soluble.



Benzoic acid.

Benzoic acid is widely distributed through the vegetable kingdom and constitutes the peculiar principle of the true balsams, such as

balsam of Peru, balsam of Tolu, and benzoin. These balsams contain also an allied substance, cinnamic acid, which resembles benzoic acid in its therapeutic properties.

Benzoin is the concrete juice of *Styrax benzoin,* a large tree, native of Siam. The drug is said to be obtained by incising the tree and allowing the juice to harden as it exudes. The finest specimens of benzoin consist of tears agglutinated together; the poorest, of brown or blackish masses without tears. The fracture is resinous, the surface of the tears smooth and whitish, the odor fragrant, the taste at first very slight, afterwards somewhat acrid. The chief constituents of benzoin are resin and benzoic acid; cinnamic acid is also frequently present. Benzoin usually contains from fifteen to twenty per cent. of benzoic acid.

Official Preparations:

Tinctura Benzoini (20 per cent.)	½ to 1 fluidrachm (2–4 mils).
Tinctura Benzoini Composita (10 per cent.)	1 to 2 fluidrachms (4–8 mils).
Acidum Benzoicum	10 to 30 grains (0.6–2 Gm.).
Ammonii Benzoas	10 to 30 grains (0.6–2 Gm.).
Sodii Benzoas	10 to 30 grains (0.6–2 Gm.).

Physiological Action.—Locally benzoic acid is markedly irritant to mucous membranes, although its salts are quite bland. It is absorbed rapidly and eliminated through the kidneys as hippuric acid.*

General Effects.—The influence of benzoic acid upon the general system is very slight. The largest therapeutic doses never produce any symptoms, unless it be those of slight gastric irritation; a half-ounce of the acid taken by Schreiber in two days caused only an increased rapidity of the pulse-beat and moderate disturbance of digestion. Some authorities believe, however, that benzoic acid exercises an effect upon nutritive processes, but the testimony as to its action upon the elimination of urea and uric acid is too contradictory to allow of definite conclusions.

Although less actively germicidal than phenol benzoic acid excels the latter as an antiseptic; according to several authorities, 1 part of benzoic acid in 2,000 is sufficient to inhibit putrefaction, and 1 in 400 will prevent the multiplication of pus cocci.

While there is some difference of opinion as to the antiseptic power of the benzoates, it is evident that they are very greatly inferior to benzoic acid. Herter states that sodium benzoate as dilute as ⅕ of 1 per cent. has a distinctly inhibiting effect upon bacterial growth, but Doepner finds that a 1 per cent. solution had but a slight retarding influence.

Therapeutic Uses.—Benzoic acid has been used as an antiseptic in various inflammations of the mucous membranes, especially of the mouth. It is, however, extremely irritant if used in concentrations

* Hippuric acid is found in considerable quantities naturally in the urine of certain herbivora, especially the horse—whence its name. At one time horses' urine was used as a commercial source for benzoic acid, but as so prepared it usually had an unpleasant odor.

sufficient to exercise any real bacterial influence, and the non-irritant salts are too feeble to be of any service.

The benzoates have been used in the treatment of inflammatory rheumatism. There is very strong authority as to their beneficial influence. Although they are inferior to the salicylates, in cases where the latter cannot be employed benzoates are useful substitutes.

Ammonium benzoate is a valuable drug in the treatment of cystitis. If the urine is acid in reaction a portion of the benzoic acid will be liberated and exercises a powerful antiseptic effect, but more than this, it appears to possess the power of acidulating the urine in cases of alkaline cystitis. Whether this effect is due to the prevention of fermentative decomposition in the bladder or to the fact that the ammonia is sometimes excreted as nitric acid is as yet uncertain.

The balsamics exert a peculiar stimulant action upon the skin; tincture of benzoin is very widely used in such conditions as chapped hands, lips, and nipples.

The question of whether the benzoates when used as food preservatives are injurious to the health is one which cannot be considered definitely settled. The present evidence goes to show that sodium benzoate is in ordinary quantities not injurious to healthy individuals, but, on the other hand, sodium benzoate in the quantities used is without preservative effect. Its value as a food preservative appears to depend upon the fact that the acids of the food decompose it, liberating free benzoic acid, which is preservative, but also irritant to the stomach. It follows, therefore, that in any foodstuff in which sodium benzoate acts as a preservative it is also liable to act as an irritant to the stomach, and, therefore, the use of this agent is one which should be discouraged.

Cinnamic acid appears to resemble benzoic acid in its physiological and therapeutic properties, although less efficient as a disinfectant; according to Rideal a 2 per cent. solution acts antiseptically, while in 4 per cent. it is germicidal. Sodium cinnamate under the trade name hetol was once lauded as a specific for tuberculosis, but is of value merely as a symptomatic remedy and is probably inferior to creosote. The dose is from $\frac{1}{6}$ to 1 grain, usually administered by intramuscular injection.

TRINITROPHENOL.

By the action of fuming nitric acid upon many organic substances there is formed trinitrophenol ($C_6H_2(OH)(NO_2)_3$), also known as *picric acid*. Commercially this body is prepared by the nitration of phenol itself. Trinitrophenol occurs as golden yellow crystals, soluble in 80 parts of water or 12 parts of alcohol. It is largely used in the arts as a dyestuff and as an explosive.

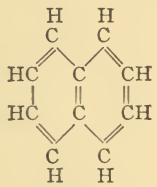
Trinitrophenol is actively astringent and a powerful germicide. According to the experiments of Schamberg and Kolmer, it is four times as actively bactericidal as phenol. Taken internally in toxic doses it produces staining of the skin, often with burning and itching, irritation of the alimentary tract, as shown by vomiting and diarrhœa, discoloration of the urine, convulsions, and, under some conditions, destruction

of the red blood-cells. It is probable that systemic poisoning may result from the too free external application.

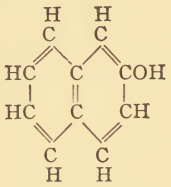
Picric acid has been used internally in the treatment of malaria, in doses of ½ to 1 grain, but is of very questionable service. Externally it is a useful local application in various skin diseases, such as acute eczema, herpes labialis, and intertrigo. It has, however, been especially lauded as a surgical dressing for burns and other ulcers. For the latter purpose a saturated aqueous solution, containing approximately 1 per cent., may be employed.

BETANAPHTHOL.

Naphthalene, which is obtained by the fractional distillation of coal-tar, may be regarded as the condensation of two benzene rings. It occurs in white, shining flakes insoluble in water, and, under the name of tar camphor, is largely used for preventing the depredations of insects in woollen clothing, natural history museums, etc. It was at one time used in medicine, but has been almost completely superseded by its hydroxyl derivative, betanaphthol. Two hydroxides of naphthalene are known, alpha- and betanaphthol, but only the latter is recognized by the U. S. Pharmacopœia. Betanaphthol is found in small quantities in coal-tar, but is usually prepared artificially from naphthalene. It occurs as colorless or pale buff crystalline laminæ, or a powder, with a pungent but not persistent taste and a faint odor.



Naphthalene.



Betanaphthol.

Betanaphthol requires 950 parts of water to dissolve it, but is soluble in less than its own weight of alcohol or of ether.

Therapeutic Uses.—Because of its sparing solubility betanaphthol is absorbed from the intestinal tract but very slowly and it seems even after its absorption to have comparatively little effect upon the system. The toxic dose for the lower animals has been estimated at 0.25 Gm. per kilo, which would correspond to a dose of about 250 grains for a man. It has, however, a marked effect upon the activity of the digestive enzymes, and when used for long periods of time is liable to produce digestive disturbances.

Although betanaphthol is so slightly soluble in water that it scarcely comes into consideration as a surgical germicide, it is one of the most powerful agents of this group. Bechold has found that 1 part in 4000 will kill the staphylococci after 24 hours' exposure, and, according to Schneider, a mixture of equal parts of naphthol and soda made an

aqueous solution which was twice as active a disinfectant as lysol. In the experiments of Maximovitch, 1 part in 10,000 of naphthol prevented the development of all the micro-organisms tested, including the anthrax bacillus, typhoid bacillus, the pus cocci, and others, while in the experiments of Sternberg 1 to 16,000 prevented the development of the cholera spirillum. According to the latter authority, the alpha- and betanaphthols have approximately the same powers as disinfectants.

Naphthol has been used externally in the treatment of various diseases of the skin. Kaposi uses a 2 per cent. soap, and states that a one per cent. solution is too irritant to be borne by the ordinary skin. It is employed as a stimulant and parasiticide in scabies, chronic eczemas, favus, and allied diseases. Internally, in doses of two or three grains, it is one of the most efficient gastro-intestinal antiseptics we possess and is useful in gastritis, enteritis, tympanites and similar conditions. It is also a valuable remedy for the treatment of hookworm; according to Schultz it is somewhat less efficient than thymol but much less poisonous. The anthelmintic dose is from fifteen to thirty grains (1–2 Gm.); repeated in about an hour and followed by an active cathartic.

SALICYLIC ACID.

Materia Medica.—Salicylic acid in the form of various esters is found in a large number of fruits and plants. Formerly it was manufactured from salicin (a glucoside found in willow bark) or from the oils of sweet birch or wintergreen, but to-day the great bulk of the commercial supply is prepared from phenol, although small quantities are still made from various vegetable sources. The terms "natural" and "synthetic" salicylic acid are used to distinguish between the salicylic acid of these sources. It is improbable that there is any difference in composition or effect between a pure synthetic or natural acid.

Salicylic acid occurs in the form of long, acicular crystals or as a dull whitish powder with a faint, aromatic odor and a characteristic unpleasant taste. It is but sparingly soluble in water, requiring more than three hundred times its weight of water to dissolve it at ordinary temperatures, but is readily soluble in alcohol. It forms with a number of alkalies salts which are freely soluble in water. Of these there are official the sodium, ammonium, and strontium salicylates, all occurring as white powders with the characteristic unpleasant taste of salicylic acid, freely soluble in water and fairly soluble in alcohol. Besides these salts various esters of salicylic acid are also used, of which two are official, methyl and phenyl salicylic esters.

Methyl salicylate is an almost colorless but slightly yellow liquid, volatile, with a very penetrating characteristic odor like that of wintergreen. It occurs naturally in a large number of plants, but is especially abundant in the wintergreen and sweet birch. The volatile oils of these two last plants contain in the neighborhood of ninety per cent. of methyl salicylate, to which substance they owe both their physical and their therapeutic properties.

Salicin is a glucoside obtained from several species of willow and poplar. It occurs as colorless crystals without odor and having a very bitter taste, soluble in twenty-one parts of water. Its therapeutic virtues depend chiefly upon the fact that it is decomposed with the formation of a sugar-like body and salicylic acid.

Official Preparations:

Acidum Salicylicum	5 to 15 grains (0.3–1.0 Gm.).
Ammonii Salicylas	5 to 20 grains (0.3–1.5 Gm.).
Sodii Salicylas	5 to 20 grains (0.3–1.5 Gm.).
Strontii Salicylas	5 to 20 grains (0.3–1.5 Gm.).
Phenylis Salicylas	5 to 15 grains (0.3–1.0 Gm.).
Methylis Salicylas	5 to 20 minims (0.3–1.2 mils).
Salicinum	15 to 30 grains (1–2 Gm.).

Physiological Action.—*Locally.*—Salicylic acid itself is very irritant to the mucous membranes and also to an extent when applied over skin surfaces. On the latter it exercises a peculiar effect, causing a softening and, finally, separation of the horny layer of the epidermis. The neutral salts of salicylates are almost free from local irritant effects.

As a germicide salicylic acid equals, if it does not surpass, in power, phenol. Kolbe found that 0.04 per cent. had great influence in preventing souring of milk. Buchholz states that 0.15 per cent. is sufficient to prevent the development of bacteria in ordinary organic mixtures, and that the influence of 0.005 per cent. is plainly visible; 0.3 to 0.4 per cent. of the acid killed bacteria in vigorous growth. In the author's experiments solutions of 0.5 per cent. destroyed the *Bacillus coli* in ten minutes; but the neutral salts of salicylic acid were not germicidal in four per cent. solution.

Digestion.—The nausea and indigestion which often interfere with the usefulness of salicylic acid and its compounds are not due to the irritant action of the drug so much as to an influence of the salicylate on the action of the digestive ferments; even when the salicylates are not administered during digestion, it is probable that they are excreted continuously into the stomach and exert their specific action.

Miller found that one per cent. of salicylic acid was sufficient to check the action of ptyalin upon starch; for the same effect ten per cent. of carbolic acid was required. The digestive action of pepsin, outside of the body, was very seriously affected by 0.02 per cent. of salicylate acid in Miller's studies, but in Kolbe's experiments the ingestion of twenty grains a day of the drug had no demonstrable effect.

Nutrition.—It seems well established that the salicylates increase to a very great extent the elimination of urea and uric acid. In the experiments of Kumagawa, the uric acid was increased in the healthy dog from thirty to seventy-four per cent. There was also marked increase in the elimination of sulphur compounds, although the relation between the elimination of nitrogen and sulphur, which in the normal animal is fixed, was distinctly disturbed.

The increase in the output of uric acid produced by salicylic acid appears to be due to greater permeability of the kidney rather than to increased formation, since the proportion of uric acid in the blood is diminished.

Nervous System.—Even in large dose the salicylates have no perceptible influence on the motor system, but they act in the same manner as the coal-tar analgesics (see p. 137) in relieving pain, although generally inferior in power. It is possible, also, that the ringing in the ears caused by toxic doses is due to some action on the auditory nerves. They also act like the coal-tar derivatives in lowering febrile temperature.

Elimination.—Salicylic acid, whether taken in the acid form or as a salt, probably circulates in the blood as a sodium salicylate. It has been shown, however, that when the percentage of carbonic acid in the blood is increased, as in asphyctic states, at least a part of the acid may be free in the blood.

The greater portion of the salicylate in the blood unites with glycocol, forming a substance known as salicyluric acid (analogous to the hippuric acid formed from the benzoates), although a part appears to escape unchanged. While the major part escapes through the kidneys, salicylic acid has been found also in the saliva. After large doses the urine often acquires a greenish hue, apparently from the formation of pyrocatechin.

Therapeutic Uses.—The most important use of the salicylates is in the treatment of various rheumatic conditions. The term rheumatism has been used so indefinitely that it is necessary to discuss separately the various types of inflammations in relation to these drugs. In rheumatic fever—acute inflammatory rheumatism—the salicylates are probably the most valuable remedies we possess. How they act is uncertain; three theories have been suggested.

The first of these explanations is that their effects are only symptomatic. That they merely relieve the pain and fever by virtue of their influence on the central nervous system is, however, manifestly untenable. Not only are the coal-tar antipyretics—which are far more powerful as analgesics and antipyretics—greatly inferior to the salicylates in rheumatism, but the clinical evidence is strong that at least in many instances they exercise an influence on the course of the disease. When the uric-acid theory of rheumatism held sway an explanation of the mode of action of the salicylates was found in their effect in increasing the elimination of this substance. But to-day uric acid is regarded rather as a result than a cause of rheumatic fever, so that this theory does not fit in with modern ideas of etiology.

The most reasonable explanation of their mode of action is that they exercise a direct antiseptic influence upon the causative microorganisms. Although sodium salicylate is too feebly antiseptic to permit of the introduction of a sufficient quantity of it into the blood to exercise any antibacterial influence, it is not at all improbable that

in the congested joints of rheumatic fever there is sufficient accumulation of carbonic acid to lead to a local decomposition of the salt and the liberation of free salicylic acid, which is an active antiseptic. According to this theory there is no difficulty in explaining the fact that it is of no value in septic infections.

In so-called muscular rheumatism the salicylates will nearly always at least relieve the pain, and in many cases will apparently produce a complete symptomatic cure. How they act under these circumstances it is impossible to form any rational hypothesis because of our ignorance of the cause of the malady.

In gonorrhœal arthritis and in arthritis deformans the salicylates are of no service. In true gout they are likewise of very little value, although in the allied forms of metabolic disturbances known as lithæmia they are at times apparently of more or less utility.

In many forms of eye diseases, such as iritis, keratitis, or glaucoma, much benefit is often derived from the use of the salicylates in full doses; indeed, their effect in numerous instances seems to be curative. Also in certain cases of diabetes they may prove of value.

As an external germicide salicylic acid is not generally available, because of its relative insolubility and its local irritant action, and the neutral salts are, as pointed out previously, greatly inferior in their antibacterial power. Salicylic acid has the power of softening epithelium and is much employed in skin diseases characterized by an overgrowth of the horny layer of the skin, notably in corns.

Administration.—In rheumatic disorders, especially the acute forms, it is usually necessary to give the remedy in full dose. Much better results are obtained by administering it in large dose until ringing in the ears, which is a sign of physiological saturation, is obtained and then stopping until the system has cleared itself of the excess, and repeating the treatment if necessary, than in using continuous small doses.

Salicylic acid itself is too irritant to mucous membranes for internal use. The salt which I have found most frequently efficacious is the ammonium salicylate. The oil of gaultheria contains approximately 90 per cent. of methyl salicylate, but, although frequently prescribed, the sources of its manufacture are so nearly exhausted that it is doubtful whether the genuine article is dispensed; the oil of sweet birch is, however, therapeutically equivalent and equally pleasant to take. There is no sufficient reason for believing that the salicylates of vegetable origin are superior to those prepared synthetically.*

Because of the tendency of all the salicylates to derange digestion they are often administered endermically. For this purpose the methyl salicylate may be mixed with an equal amount of some fatty substance, as lard or cotton-seed oil, about a drachm of the mixture painted over

*It was at one time believed that cresotinic acid, which sometimes occurs as an impurity of synthetic salicylic acid, was poisonous, but Stockman (J. P. and Ex. T., 1912, iv) has not only shown that it is no more poisonous than salicylic acid but that it exercises the same type of beneficial influence in rheumatic fever.

an area of twelve square inches and covered with some impermeable dressing, as oiled silk.

Aspirin (*Acetyl-salicylic Acid*) occurs in white, crystalline, insoluble needles, of an agreeable taste, which undergo decomposition in alkaline fluids with the separation of salicylic acid, and are therefore changed by the intestinal secretions.

Although the urine shows the presence of salicylic acid within half an hour after the ingestion of aspirin, it is probable that the drug circulates, at least in part, unchanged, for the effects are in some ways quite different from those of the salts of salicylic acid. Although in full doses it may produce cinchonism and the other symptoms of salicylic acid poisoning, there have been reported a number of cases in which relatively small quantities have produced quite different symptoms. In these cases there has been generally more or less cardiac weakness with rapid or irregular pulse and profuse sweating; in many instances there has been an extraordinary œdema of the face and of the mucous membrane of the mouth and throat.

As an anti-rheumatic, acetyl-salicylic acid is certainly inferior to the salicylates, but it has much more powerful analgesic and antipyretic properties, approaching, in these regards, the acetanilid group. It is frequently of value in the treatment of subacute and chronic cases of rheumatic origin, for the reasons that it is usually better borne by the stomach and is probably more slowly eliminated than the inorganic salicylates, therefore more continuing in its effects. It has also been employed for the relief of neuralgic headaches and similar painful states. Fetterolf has highly recommended the local use of powdered aspirin in acute tonsillitis.

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FORMALDEHYDE.

Formaldehyde (HCHO), *formyl* or *formol,* is a gaseous body which is obtained by the oxidation of methylic alcohol at moderately high temperature, as by passing the vapors over red-hot metal or carbon. It readily dissolves in water and alcohol, forming a colorless fluid, with a peculiar, pungent odor and an unpleasant taste.

Under various conditions three molecules unite to form the polymer trioxymethylene, which is recognized by the Pharmacopœia under the name of paraformaldehyde. The official solution of formaldehyde (*liquor formaldehydi*) contains not less than 30 per cent. by weight of the gas.

Physiological Action.—*Local Action.*—Formaldehyde is an intensely active local irritant, producing even when in very minute amount in the air violent irritation of the respiratory mucous membrane,

or, it may be, fatal pulmonary inflammation. It is also a very active coagulant of albumin and gelatin when in at all concentrated form; and when added to blood it causes an immediate coagulation, with a serum so strongly colored red as to suggest destruction of the red blood-corpuscles, though it may be that the color is due simply to the squeezing out of the corpuscles from the clot. According to Mosso and Paoletti, however, when added in a very dilute form to an albuminous solution, formaldehyde not only does not coagulate the albumin, but so acts as to prevent the coagulation of albumin by heat. It is therefore capable of absorption, and the statements made that the urine passed by animals to which it is given even in moderate quantities is incapable of putrefaction indicate that it is not only absorbed but also eliminated unchanged from the kidneys.

General Effects.—Formaldehyde is a very feeble substance so far as its general effects on the system. Mosso and Paoletti have found that 50 C.c. per kilogram injected intravenously into the dog produced collapse, with marked fall of temperature, ending fatally after several days. The same authors also find that small doses cause a rise in the blood-pressure, probably through constricting the blood-vessels, and toxic doses lower the pressure and increase the coagulability of the blood.

When taken by the mouth, however, relatively small quantities produce very marked effects. These symptoms are to be attributed to the local irritant action upon the gastric mucous membrane.

Disinfectant Action.—Formaldehyde is unique among antibacterials in that it is more powerful in the form of vapor than when in aqueous solution. A solution of formaldehyde is scarcely more actively bactericidal than a solution of corresponding strength of phenol.

According to Burgess, a two per cent. solution of formaldehyde kills the bacillus coli communis in five minutes. In the experiments of Slater and Rideal it required fifty minutes for a one per cent. solution to kill the staphylococcus pyogenes aureus or bacillus typhosus, and thirty minutes to destroy the bacillus coli communis.

As an antiseptic, however, the solution of formaldehyde is efficient in extreme dilution. In Slater and Rideal's experiments, one part of formaldehyde in 5,000 was sufficient to absolutely restrain the growth of all forms of bacteria, and one portion in 20,000 markedly inhibited the multiplication of many species of organisms.

As regards the effect of the vapor of formaldehyde, the above-quoted investigators found that a quantity of formaldehyde equivalent to 0.032 per cent. showed a marked destructive action on many forms of organisms, but did not completely sterilize the air.

Kenwood has determined that when formaldehyde vapor is present in the air in the proportion of one and one-half to two per cent. there is complete and rapid disinfection of all the surfaces. Woodhead found that the vaporization of one pound of forty per cent. formaldehyde solution, by means of a special form of apparatus, destroyed all

exposed cultures in an ordinary bedroom, including the spores of the anthrax bacillus, but that pieces of folded linen were not always completely sterile. In a lamp generating formaldehyde directly from methyl alcohol, according to Kenwood, it requires one and one-half litres of alcohol to disinfect a room of two thousand cubic feet. A popular and convenient form of formaldehyde generation is through the heating of tablets of *paraformaldehyde*. According to Rideal, four grammes of paraform per thousand cubic feet of air space killed the test-germs which were exposed on silk threads, but not cultures soaked into paper slips; ten grammes of paraform per one thousand cubic feet killed various non-sporing micro-organisms, both exposed and when wrapped inside of rolls of linen; the spores of the anthrax bacillus and bacillus subtilis were usually, but not invariably, destroyed by twenty grammes per thousand cubic feet.

An abundance of moisture in the air is essential for the best effects of formaldehyde.

Therapeutic Uses.—Because of its highly irritant properties formaldehyde is rarely of value as a surgical disinfectant except for the purpose of sterilizing instruments. It is, however, sometimes employed as an external antiseptic in various skin diseases and is also a valuable agent in the treatment of hyperhidrosis, in which disease it not only prevents the production of disagreeable odors from the decomposition of the sweat, but by its hardening effect upon the skin lessens the tendency to excessive secretion. Because of its safety and its lack of destructive action on vegetable and animal substances and its powerful germicidal effect, and of the fact that, having practically the same specific gravity of air, it penetrates readily through loose fabrics, the vapor of formaldehyde is unrivalled for the purpose of disinfecting the sick-room after contagious diseases.

In disinfecting an apartment, windows, doors, chimneys, ventilators, and similar openings should be tightly closed, while the air should be made to contain at least one per cent. of formaldehyde gas, and at the end of twenty-four hours, when the apartment may be opened, should still be strongly impregnated.

A number of apparatuses for the generating of formaldehyde for the purpose of disinfecting rooms are upon the market. All of these act on one of three principles: first, by the oxidation of vapors of methyl alcohol; second, by the evaporation of the aqueous solution of formaldehyde; third, by decomposition of the polymer known as paraform. The most popular of these to-day, however, is the vaporization from the aqueous solution. This is accomplished in a variety of ways. Boards of health in some places, for instances, simply sprinkle a solution of formaldehyde liberally over the floor and walls of the apartment with an apparatus similar to that which is used for spraying plants. The greatest drawback to this method is the deleterious action upon the mucous membrane of the operator. In other types of

apparatus the solution of formaldehyde is vaporized from a boiler by means of heat and is carried into the room through a small tube which may be inserted through the keyhole. Of recent years there has come into use a very cheap and handy method for generizing formaldehyde vapors which depends upon the fact that when certain substances, notably potassium permanganate, are brought in contact with a solution of formaldehyde there is generated an intense heat; indeed, so intense is the heat generated under these conditions that certain authors have warned against the possibility of fire unless the vessels used are amply large. For an ordinary-sized room the following proportions have been recommended: one quart of a solution of formaldehyde, one pound of potassium permanganate, and one quart of water, and a vessel, or vessels, of at least twenty-five quarts capacity. The potassium permanganate is first placed in the tub and the mixture of equal parts of solution of formaldehyde and water poured over it, the room having previously been tightly closed. It should then be left shut for a period of at least six hours. A similar method has been employed in which lime is used instead of permanganate.

Poisoning.—Several cases of serious, and even fatal, poisoning have been recorded as due to formaldehyde solutions. The symptoms have generally been epigastric pain, generally with vomiting of blood-stained mucus, usually collapse with loss of consciousness, a rapid feeble pulse, with albuminuria and often bloody or suppressed urine. The vomitus and sometimes the fæces have a strong odor of formaldehyde. In the fatal cases the dose was about three ounces of the commercial solution. In post-mortem there was found an acute gastritis and the stomach walls were tanned to a leather-like constituency. There was also evidence of irritation of the liver and of the kidney. The treatment should be evacuation, the use of ammonia as antidote, and stimulation as indicated.

HEXAMETHYLENAMINE.

Hexamethylenamine-tetramine is a condensation product of ammonia and formaldehyde largely employed in medicine under various trade names, as urotropin, formin, cystogen, etc., and recognized by the United States Pharmacopœia as hexamethylenamine. It is a crystalline substance, colorless and odorless, with a bitterish sweet taste, soluble in one and one-half times its weight of water and in ten parts of alcohol. Its aqueous solution reacts alkaline to litmus. When warmed with dilute acids it is decomposed in the ammonia and formaldehyde.

Physiological Action.—Locally, hexamethylenamine is quite actively irritant, although much less so than formaldehyde. It is absorbed rapidly through mucous membranes and has been detected in almost every fluid of the body, including the blood, the bile, the

cerebrospinal fluid, the bronchial secretions, etc. It is eliminated chiefly through the kidneys, although it is probable that all of the excretory glands aid in its elimination. It passes out of the kidney probably entirely unchanged, but if the urine be acid it is slowly decomposed in the bladder, liberating free formaldehyde. The question of whether formaldehyde can be split off in any other of the bodily secretions is one to which a positive answer cannot at present be given. On the one hand Hanzlik, after examination of a large number of normal and pathological secretions, reached the conclusion that free formaldehyde could occur in none of them except the urine because of their universal alkalinity. On the other hand are indubitable clinical results which can hardly be explained on any other grounds than its decomposition, and the observations of Sachs, who found free formaldehyde in the blisters of various bullous skin diseases after its administration.

Jordan has shown that the antiseptic properties of hexamethylenamine itself are only moderate, a 1 per cent. solution being required to inhibit the growth of micro-organisms in neutral or alkaline media. On the other hand, in acid fluids, even although the degree of acidity is relatively low, it exercises a very powerful restraining influence upon the growth of bacteria, due to the liberation of formaldehyde. The proportion of formaldehyde which will be given off, and hence the degree of antiseptic power of the drug will be increased with the increasing degree of acidity within certain limits.

General Effects.—The general action of hexamethylenamine is very similar to that of formaldehyde. Like the latter, it is not a substance of great physiological power, and large quantities can be administered that the fatal dose for the guinea pig is about five grains for each ounce of body weight. Fleig has found that it produces at first a slight vasodilatation of the renal vessels, followed, at the end of five to twenty minutes, by a violent constriction, which lasts for several hours; there was no effect upon the general blood-pressure.

Therapeutic Uses.—Hexamethylenamine was originally brought forward as a solvent for uric acid, but its use for this purpose has been practically abandoned. It is employed to-day chiefly as an internal antiseptic, especially for the urinary tract. When the urine is acid in reaction it is without doubt the most powerfully acting antiseptic we possess. On the other hand, in cases where this secretion is alkaline its restraining influence upon bacterial growth is very slight. In those forms of cystitis in which ammoniacal decomposition of the urine occurs in the bladder, unless it be possible by the administration of acid phosphate of sodium or by some other measure to render the urine acid, hexamethylenamine is not only an inferior remedy to many urinary antiseptics but may prove actually harmful because of its local irritant action upon the cystic mucosa.

In 1908 Crowe demonstrated the occurrence of formaldehyde in the gall-bladder after the administration of hexamethylenamine, and reported remarkable results in infections of the gall-bladder following typhoid fever. His conclusions as to the clinical value of this treatment have been confirmed by a number of authors, and the principle extended to infections of other secretions.

The demonstration that hexamethylenamine is found in various other secretions of the body has led to its employment in a large number of infectious conditions. Thus, in the very common infection known as "cold," whether involving the nasal mucous membrane or appearing in the form of acute bronchitis, it has been found that, if used in the formative stages of the infection, a very large proportion of the cases can be aborted. In the author's experience but little result in acute coryza has been obtained from the drug unless administered within twenty-four hours after the appearance of the earliest symptoms. It has also been employed in cerebrospinal meningitis with the idea that it could restrain the growth of micro-organisms in the spinal canal, and the experiments of Flexner and Clark suggest a possible usefulness in epidemic poliomyelitis.

The ordinary dose of hexamethylenamine is ten to twenty grains three or four times a day, which should be given preferably in solution and well diluted to avoid irritation of the stomach. After large quantities of the drug a variety of unpleasant symptoms have been observed, such as ringing in the ears, headache, eruptions on the skin, and hæmaturia.

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SULPHUR.

Sulphur occurs, uncombined, in the neighborhood of volcanoes, either extinct or active. Large deposits of this nature are located in the island of Sicily and in various places in the United States, especially in California and Louisiana. It is also found in combination with various metals such as iron (pyrite), mercury (cinnabar), etc. The crude sulphur obtained, either by heating sulphur-containing minerals or directly from the sulphur mines, is purified by subliming. This occurs as a fine yellow powder, sometimes known as "flowers of sulphur." This sublimed sulphur, after being further purified by washing it with ammonia and water, is the *Sulphur lotum* of the Pharmacopœia. *Precipitated sulphur* (milk of sulphur) is made by boiling lime and sulphur and then decomposing the calcium sulphide formed with hydrochloric acid and washing the precipitate. It is of somewhat lighter color than the other forms of sulphur, and, because of its extreme state of subdivision, is especially suitable for suspension in liquids. Sulphur is insoluble in water or alcohol, but in aqueous solution of the caustic alkalies forms soluble sulphides. It is dissolved unchanged by the fixed oils or oil of turpentine. It is inflammable.

Sulphurated lime, or crude calcium sulphide, is made by heating together calcium sulphate and charcoal; it is a grayish powder with a faint odor of hydrogen sulphide and a disagreeable alkaline taste, almost insoluble in water and undergoing spontaneous decomposition on exposure to air. It consists of at least 55 per cent. of calcium sulphide (CaS) and varying qauntities of gypsum and charcoal. *Sulphurated potassa* is made by heating together potassium carbonate and sulphur, and is a mixture of various sulphides of potassium with potassium thiosulphate. It forms brown pieces which are freely soluble in water and are decomposed by exposure to air. It has a strong odor of hydrogen sulphide.

Sodium thiosulphate ($Na_2S_2O_3$) is sometimes incorrectly known as sodium hyposulphite. The latter salt ($NaHSO_2$), however, has very different properties, being an active reducing agent, which the thiosulphate is not. Sodium thiosulphate occurs as large, colorless crystals freely soluble in water, with a salty bitterish taste. Neither it nor the normal sodium sulphite (Na_2SO_3), which is also official, has been shown to possess any very active therapeutic properties.

Official Preparations:

Sulphur Sublimatum	As an alterative, 10 to 20 grains (0.6–1.2 Gm.).
Sulphur Lotum	As a laxative, 1 to 2 drachms (4–8 Gm.).
Sulphur Præcipitatum	As a laxative, 1 to 2 drachms (4–8 Gm.).
Unguentum Sulphuris (15 per cent.)	External use.
Calcii Sulphidum Crudum	⅓ to 1 grain (0.02–0.06 Gm.).
Potassa Sulphuratum	Not used internally.
Sodii Sulphis Exsiccatus	10 to 20 grains (0.6–1.2 Gm.).
Sodii Thiosulphas	10 to 20 grains (0.6–1.2 Gm.).

Physiological Action.—Sulphur itself is medicinally inert. When burned in the air it unites with the oxygen to form sulphurous anhydride, which is actively germicidal. When taken into the intestinal tract it is partially dissolved by the alkaline secretions, and the alkaline sulphide formed is later broken up with the formation of hydrogen sulphide, which by its local irritant action increases intestinal peristalsis and causes catharsis. A similar change is brought about by the sweat when sulphur is applied to the skin.

Therapeutic Uses.—Sulphur has been used internally as a laxative, but, although some of the older writers recommend it highly in the treatment of chronic rheumatism, it is very doubtful whether it possesses any special virtues which do not belong to the other cathartics. Because of the formation of hydrogen sulphide, it exercises, in the intestinal tract, more or less antiseptic action, and has been commended as an intestinal antiseptic in typhoid fever and in dysentery.

The most important therapeutic use of sulphur and its compounds is externally in various skin diseases. The hydrogen sulphide which is formed is an active germicide and parasiticide and is therefore useful in parasitic diseases, such as scabies, ringworm, tinea versicolor, etc. Moreover, the alkaline sulphides have solvent properties towards the horny elements of the skin, and the sulphur compounds are therefore useful in those conditions, such as psoriasis, in which there is excessive scale formation; probably for the same reason they are useful for depilatories. By virtue of their reducing effects the sulphides exercise a stimulant action on the circulation of the skin and encourage the formation of new epidermis, and for this reason are useful in acne or seborrhœa. The calcium or potassium sulphides are more active agents than the elemental sulphur, as the chemical reaction necessary for the effects of sulphur has, in part, already taken place.

Although the acid sodium sulphite, formerly recognized as sodium bisulphite, because of the slow evolution of sulphurous acid gas possesses marked antiseptic properties, the neutral sodium sulphite does not, and there seems to be no proper reason for the retention of this substance in the Pharmacopœia. Sodium hyposulphite—familiar to the photographer as "hypo"—has strong reducing properties and may therefore be useful in scaly diseases of the skin; the official thiosulphate, which is sometimes confused with it, does not appear to possess any remedial virtues.

While sulphurous oxide formed by burning sulphur under proper conditions is capable of acting as a disinfectant, the custom of burning sulphur candles in the sick-room is of no practical service. In the first place, for an ordinary room of two thousand cubic feet of air space it would require some three pounds of sulphur to generate sufficient gas, and, secondly it is necessary that the air be saturated with aqueous vapors, as the gas is inactive in the absence of moisture. These conditions can only be fulfilled with special apparatus. Sulphur dioxide is also useful for ridding rooms of insect vermin.

ICHTHYOL.

By treating the distillate of a bituminous shale which is found in the Tyrol, with sulphuric acid, there is formed a body known as ichthyol-sulphonic acid. The substance commonly known as ichthyol is obtained by neutralizing this acid with ammonium carbonate and is therefore really an aqueous solution of ammonium ichthyol-sulphonate. It is a brown, syrupy liquid with a characteristic bituminous odor, miscible in all proportions of water but only partly soluble in absolute alcohol. It contains about 10 per cent. of sulphur of which about one-half is present as a sulphonic acid and one-half in organic combination.

There are a number of compounds more or less similar in nature to ichthyol which have been brought forward; among these may be mentioned *thiol,* which is made by treating certain paraffine oils with sulphur, then sulphuric acid; *thiginol,* which is the sodium salt of sulpho-oleic acid; *bituminol,* which is obtained from a bituminous product in a manner exactly similar to that of ichthyol.

Ichthyol has a mild antiseptic action. According to experiments of Abel (1893) it is especially effective against streptococci; he found that while a solution of one part in 200 destroyed streptococci in 24 hours, that it required five hours for pure ichthyol to kill staphylococcus aureus. It is antiseptic in strengths ranging from one-fifth to five per cent., according to organism against which it is tested. It is capable of passing through the skin and by some is believed to exercise a local vaso-constrictive effect. When taken internally it exercises a mildly stimulating action on the intestinal tract. It is extremely doubtful that it has any systemic effect of therapeutic value.

Ichthyol is used to a very large extent as a remedy for all kinds of inflammatory conditions of the skin, such as acne, chronic eczema, and even erysipelas. It is especially prized in furunculosis. Its mode of action in these cases is at present entirely inexplicable; some attribute the results to an antiseptic influence while others believe it affects the local nutrition. It has also been employed in more deeply seated inflammations, such as sprains, rheumatism, myalgias, or frost bite. If it possesses any virtue in these latter conditions it is probably simply that of a mild counterirritant.

Internally it is occasionally employed in the treatment of pulmonary tuberculosis. For the latter purpose it may be given in doses of 3 to 5 minims although the combination with egg albumin known as ichthalbin is generally preferred as being less prone to disturb digestion. The dose of ichthalbin is 15 to 30 grains (1 to 2 Gm.).

As a local application ichthyol is used in strengths varying from 10 to 100 per cent.

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BORIC ACID.

Under the name of boric acid the Pharmacopœia recognizes orthoboric acid $B(OH)_3$, also known as boracic acid. This is a crystalline solid soluble in eighteen parts of cold water, much more freely soluble in boiling water or in glycerine.

The Pharmacopœia also recognizes sodium borate. This substance —which is variously known as sodium tetraborate or sodium biborate and popularly as borax—is the salt of pyroboric acid and has a formula of $Na_2B_4O_7$. Orthoboric acid does not form normal salts.

Borax is obtained naturally in many parts of the world, there being several deposits in the United States. It is usually sold in the form of a white powder which is inodorous and of an alkaline taste, but can also be obtained in the form of colorless crystals. It is soluble in twenty parts of water and freely soluble in boiling water or glycerine.

There is a third acid, which is known to chemists as metaboric acid, which has the formula HBO_2. This latter substance is rarely or never employed in medicine.

Sodium borate acts as an alkali and has the same incompatibilities as sodium carbonate.

Boric acid crystallizes in white, translucent scales, soluble in eighteen parts of cold water, much more soluble in boiling water, which on cooling precipitates all but about twenty-three grains to the fluidounce. Hot glycerine dissolves and holds upon cooling as much as three drachms to the fluidounce.

Official Preparations:

Acidum Boricum	10 to 20 grains (06–1.2 Gm.).
Glyceritum Boroglycerini (31 per cent.)	External use.
Sodii Boras [Borax]	15 to 30 grains (1–2 Gm.).

Physiological Action.—Boric acid, even in saturated aqueous solution, is practically non-irritant to mucous membranes. It is freely absorbed and eliminated, escaping chiefly through the kidneys unchanged.

Boric acid and its salts are peculiarly inert physiologically; Maass asserts that sodium chloride is more toxic to the frog than boric acid. Very large doses, however, have a depressant influence upon the motor centers of the spinal cord.

Boric acid or its salts can scarcely be called germicidal. While some organisms are killed by a prolonged exposure to saturated solutions, the action of the substance is so feeble as to scarcely justify the application of the term germicidal. It has, however, a distinct antiseptic influence.

Boric acid has been employed to a considerable extent as a wash in inflammatory conditions of various mucous membranes, as in conjunctivitis, rhinitis, and cystitis. Whether the beneficial results which have followed its use are due to anything more than mechanical cleans-

ing of the part is somewhat doubtful, although many clinicians believe it exercises a peculiar stimulant alterative action upon the mucous membrane.

The use of boric acid as a food preservative is a subject of immense importance from a commercial stand-point. The financial interests involved are of such magnitude and the evidence so contradictory that one is scarcely justified at present in taking too positive a position as to the permissibility of the use of this agent. The evidence that the continuous use of boric acid for long periods of time exercises a deleterious effect upon the system is very strong, but whether it is more injurious than other food preservatives whose employment is permitted by long custom, such as potassium nitrate, is uncertain.

PRACTICAL DISINFECTION.

The uses to which disinfectants are put are too numerous to permit of a detailed consideration of them, but some of the considerations which lead us to prefer one or the other of them may be briefly set forth as guiding principles to illustrate the methods of making a choice among them. The difference between an antiseptic and a germicide may be repeated in order to be emphasized and especially to call attention to the fact that by equivalent dilutions the disinfectants are not equally weakened; for instance, in a concentration of 5 per cent. disinfectants A and B may be equal in strength, but in dilutions of 1 per cent. or ½ per cent. A may be two or three times as certain as B. Especially is this the case where a germicide is diluted below the germicidal strength down to its antiseptic strength. Thus phenol and creosote in a 1 per cent. solution are approximately equal in their germicidal powers, but a 1/10 per cent. solution of phenol is almost without antiseptic virtues, while a 1/10 per cent. solution of creosote is a very powerful antiseptic. Therefore, when a disinfectant is selected for a purpose in which it is likely to be rapidly diluted—for instance, as in making antiseptic mouth washes or washing out internal cavities, or for disinfecting the intestines—we should choose one not so much for the rapidity of its germicidal action in strong solution, but for the retention of some antiseptic power even when greatly attenuated. The germicidal strengths which have been given in the preceding pages, it must be remembered, are mostly based upon experiments made with bacteria more or less isolated, whereas in ordinary clinical use they are generally found in the midst of albuminous surroundings, and, since the majority of germicides are precipitants of albumin, their germicidal value is often partially, or even completely, negatived by the conditions under which they are employed. For this reason one must not expect so great an action clinically as results of laboratory investigation would indicate. Some of them are much more affected by the presence of organic matters than others.

The uses to which disinfectants are put may be classified as follows: For purposes not directly connected with the human body—(1) dis-

infection of surgical instruments; (2) disinfection of clothing, dishes, furniture, and the like; (3) disinfection of excreta. For use around the body—(1) cleansing of wounds and skin; (2) disinfecting accessible mucous membranes and internal cavities; (3) gastro-intestinal disinfection.

For the disinfection of surgical instruments the germicide should have the following properties: first, it should be powerfully and quickly active in appropriate solution—whether it loses its efficiency very greatly under dilution or if it is precipitated very violently by albuminous substances are matters of little moment, because we can use it in any strength solution which may be necessary and because the instruments can easily be cleansed of all gross dirt. The germicide, moreover, must be one which is not injurious to the instruments employed; this corrosive sublimate cannot be employed for disinfecting steel instruments. Among those which are peculiarly suitable for this purpose are cresol—which, in the writer's opinion, is far superior for this purpose to phenol—corrosive sublimate (except for metallic instruments); formaldehyde and alcohol are occasionally useful for special purposes in this connection, but are not so generally applicable as cresol.

The disinfection of patients' clothing or bedding and other articles of the sick-room is one of the most serious problems of hygienic economics. In the first place, many of the powerful germicides are injurious to articles which are in need of sterilization; secondly, there is often a considerable amount of organic matter which interferes with the action of the germicide. Different articles require very different treatment. For the disinfection of glassware, chinaware, and the like, which have come in contact with infected persons, there is no substance so valuable as one of the chlorine solutions, either the official solution of chlorinated soda or, better, a solution of chlorinated lime. These germicides have the advantage of being very powerful and of not losing their activity in the presence of organic material. The disinfection of woollen clothing can only be accomplished satisfactorily without injury by the use of either formaldehyde vapors or superheated steam. Bed-clothes and any other similar material which will not be injured by the process are best disinfected by boiling. In changing bedclothing a clean sheet should be laid upon the floor and into it thrown the discarded clothing and bedding, then tie the whole into a hard ball and drop it into boiling water without opening, and allow it to remain for an hour. This method has, however, the objection of fixing permanently in the muslin all stains from blood, fæces, and organic discharges. It is better, therefore, and in a hospital-ward it is essential, to throw the personal and bedclothing piece by piece when taken off directly into a covered vessel containing a disinfecting solution. According to the experiments of A. C. Abbott, corrosive sublimate is actively mordant, and should not be used. Chlorinated lime, 0.5 per cent. solution, in cold water, is effective, does not fix

stains, and though theoretically it should attack the structure of various fabrics, practically has no perceptible influence unless after repeated immersion. The official compound solution of cresol in the proportions of 5 parts in 100 is also useful. After two hours' soaking in such a mixture the clothing must be taken out and well washed in water at a temperature *not exceeding* 100° F. until all stains have been removed. The furniture, walls, and most other articles around the room may be disinfected by washing with a strong solution of cresol.

For disinfection of all excreta, sputum, fæces, or urine, the only chemical disinfectant which should ever be considered is chlorinated lime or chlorinated soda. The recommendations of many text-books advising the use of phenol as a disinfectant of excreta can hardly be too severely condemned. It coagulates albumin and is, therefore, incapable of penetrating into masses of filth. On the other hand, by virtue of its oxidizing effect and great penetrating power chlorinated lime not only disinfects the whole mass but also tends to get rid of a mass of substances which could form culture for the growth of future generations of bacteria. Further, phenol, especially in the presence of sporulating bacteria, is slow and uncertain in its germicidal powers, and is rapidly reduced by dilution. Chlorine, on the other hand, is one of the most rapid and certain germicides we possess. Moreover, chlorinated lime is a deodorant as well as a disinfectant. Finally, phenol has the disadvantage of being not only less efficient but being about fifty times as expensive in proportion to its germicidal power.

The process of purifying a room which has been occupied by a patient with an infectious disease, naturally divides itself into two parts—first, the killing of the germs; second, the cleaning of the room—and these two acts should always follow in the order here given so as to lessen as much as possible the danger to the operator and to the surrounding habitations which would be caused by the dispersion of the active germs. First, all clothing and bedding must be disinfected, and the most efficient and useful agent in so doing is heat. In cities, in quarantine stations, and other places where proper apparatus is forthcoming, all articles of the character spoken of should be exposed to the prolonged effect of hot steam in closed chambers. There are often many objects in a sick-room which it is almost impossible to reach by disinfectant solutions. The minute cracks between floors and the walls, or between the boards of the floor, the crevices around furniture, the interior of drawers in bureau and table, the backs of shelves and the hinges of doors, etc., are almost impossible to reach with bactericidal solutions. For this reason it is always desirable that a room which has been occupied by a patient suffering with contagious disease should be sterilized by one of those agents which are active in vaporous form. For this purpose by all means the best is formaldehyde.

The question of wound disinfection is such an extensive one and so purely a surgical problem that it does not seem necessary to consider it here. In the disinfection of internal cavities it is just as im-

portant that we shall use a disinfectant that will do no harm as it is to use one which is efficient. A disinfectant for this purpose should be one which is not poisonous and which is not highly irritant. Practically all disinfectants used in solution sufficiently concentrated to be powerfully germicidal are irritant to mucous membranes. It becomes of importance, therefore, in choosing an agent for this purpose, to select one which retains its antibacterial effect, at least in part, even when greatly diluted. Probably the agents which are most powerfully germicidal in proportion to their local irritant actions are the salts of the metals, mercury and silver. Unfortunately, however, these salts are mostly chemically so unstable that they are unfitted for many uses of this nature. The oxidizing disinfectants are frequently employed, such as potassium permanganate and hydrogen dioxide, but I am inclined to believe that their value is more that of cleansers than that of antiseptics. Among the agents which are frequently of service in this group are those which belong to the series of phenols.

The requisites for an intestinal disinfectant are, first, that it have a relatively low toxicity; second, that it shall retain its activity in the presence of large amounts of organic fluids. While it is possible that some of the unofficial germicides may be more efficient for this purpose, of the pharmacopœial agents the two which most nearly satisfy these conditions are betanaphthol and creosote.

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CHAPTER VIII.

EXTRANEOUS REMEDIES.

In this chapter are included those drugs whose virtue depends upon some simple chemical action modifying the secretions of the body and those substances which are used externally for their effects on the skin.

DIGESTANTS.

In cases of so-called dyspepsia the natural thought of the physician is to administer drugs which will, by virtue of their own digestive power, replace lacking digestive ferments. It is because of this natural tendency that pepsin and pancreatin are among the most widely used and most widely abused drugs in the Pharmacopœia. The careful physician remembers, in the first place, that many cases of so-called dyspepsia are not due to a deficiency in the gastric secretions, but, indeed, are combined with overactivity of these glands (hyperchlorhydria); that even when the digestive secretions are deficient it is often the result of an irritation of the gastric mucous membrane, and that the relief of this irritation will be followed by normal secretion. Even where there is a real failure of gastric digestion, pepsin, or rather pepsinogen, is but rarely lacking, the failure in digestive power being due to deficiency in acid to activate the abundant secretions of the peptic glands. The mineral acids, therefore, from the stand-point of practical therapeutics, are valuable digestants. Moreover, the gastric symptoms seen in cases of digestive failure are not so much due to the presence of undigested protein in the stomach as to the irritant products resulting from fermentation of the carbonaceous elements of the food which is permitted by the absence of the natural antiseptic of the stomach (hydrochloric acid) and to the motor deficiency which is also partly due to the deficiency in acid.

As regards the digestive ferments of animal origin, such as those known as pepsin and pancreatin, it must be remembered that these are delicate bodies whose activity is destroyed by the presence of large amounts of either acid or alkali, as well as by alcohol and many metallic salts.

ACIDS.

The presence of a mineral acid in the stomach is necessary for the activation of pepsinogen. The mineral acids are, therefore, widely used in cases of dyspepsia where there is a failure of the natural secretion of hydrochloric acid.

The value of the acids in digestive failure is, however, not due solely to their activation of pepsinogen. In the first place, the motor function of the stomach is largely governed by the relative acidity on

the two sides of the pylorus. Secondly, the physiological stimulation for pancreatic secretion with its important digestive ferments seems to be a hormone formed by the action of hydrochloric acid on duodenal epithelium. Finally, the mineral acids are powerful antiseptics and, therefore, check the fermentation which may give rise to products highly deleterious to the gastric mucosa.

Boer has found that hydrochloric acid in the proportion of 0.15 per cent. effectually restrained the growth of all bacteria with which he experimented, and that most forms were impeded by as small amounts as 1 part in 2,000 of this acid.

Materia Medica.—*Hydrochloric acid* is a colorless aqueous solution of hydrochloric acid gas, having the specific gravity of 1.158 and containing 31.9 per cent. by weight of the gas. The yellowish tint of commercial hydrochloric acid is due to the presence of ferric chloride, organic matter, or other substance.

Nitric acid is a liquid of the specific gravity of about 1.403, which as first made is colorless, but by exposure to the light acquires a yellow tint. It oxidizes all the common metals except gold, and is exceedingly corrosive to living tissue, which it stains an indelible yellow. When dilute it converts most animal and vegetable substances into oxalic, malic, or carbonic acid.

Nitro-hydrochloric acid is made by mixing nine parts of nitric acid with forty-one parts of hydrochloric acid. If the acids be sufficiently strong, an orange-colored liquid will be formed with the evolution of intensely irritating vapors.

After standing for a length of time, the *red* color of freshly mixed nitro-hydrochloric acid changes to a golden yellow. It is in this state that the United States Pharmacopœia directs the acid to be used. By longer standing the *golden* yellow becomes *lemon* yellow, and the odor of chlorine is almost entirely lost. These changes are hastened by light, but will occur in the dark and in well-stoppered bottles. This agent should always be freshly prepared.

Sulphuric acid is known popularly as the oil of vitriol. When pure it is a colorless, heavy liquid which on exposure to air rapidly absorbs moisture. The official acid contains not less than 92.5 per cent. of absolute sulphuric acid and has a specific gravity of 1.826. It mixes in all proportions of either alcohol or water with the evolution of much heat.

Phosphoric acid, which results from the burning of phosphorus in the air, is prepared by the action of sulphuric acid upon bone-ash, which consists chiefly of calcium phosphate. The official acid contains eighty-five per cent. of the tribasic acid of chemists. It is a colorless, inodorous, sour liquid, of a syrupy consistence, which has a very acid reaction, and is corrosive to animal tissues.

Hypophosphorous Acid.—The official hypophosphorous acid is a colorless liquid representing about 30 per cent., by weight, of absolute hypophosphorous acid.

Official Preparations:

Acidum Hydrochloricum (32 per cent.)	5 to 10 minims (0.3–0.6 mil).
Acidum Hydrochloricum Dilutum (10 per cent.)	15 to 60 minims (1–4 mils).
Acidum Nitricum (68 per cent.)	Not used internally.
Acidum Nitricum Dilutum (10 per cent.)	15 to 60 minims (1–4 mils).
Acidum Nitrohydrochloricum	3 to 8 minims (0.2–0.5 mil).
Acidum Nitrohydrochloricum Dilutum	15 to 30 minims (1–2 mils).
Acidum Sulphuricum	Not used internally.
Acidum Sulphuricum Dilutum (10 per cent.)	15 to 30 minims (1–2 mils).
Acidum Sulphuricum Aromaticum (20 per cent.)	10 to 20 minims (0.6–1.2 mils).
Acidum Phosphoricum	5 to 10 minims (0.3–0.6 mil).
Acidum Phosphoricum Dilutum (10 per cent.)	½ to 1 fluidrachm (2–4 mils).
Acidum Hypophosphorosum (30 per cent.)	Not used internally.
Acidum Hyphosphorosum Dilutum (10 per cent.)	8 to 15 minims (0.5–1.0 mil).

Therapeutic Uses.—Although certain of these acids, notably hypophosphorous and phosphoric, are by some supposed to exercise a favorable influence on the nutritive processes of the body, it is probable that the beneficial effects which have followed their administration is due purely to the improvement in digestion. The soluble phosphates, however, are sparingly diffusible and, therefore, useful as cathartics (see p. 269). There is no sufficient reason to believe that any of these acids possess any therapeutic virtues beyond their effects on the digestive processes.

The natural acid of the stomach is hydrochloric acid, and ordinarily, in cases of digestive failure, preference is given to this acid. It is to be remembered that a failure of the acid glands of the stomach is much more common than of the peptic glands, and therefore the usual case of dyspepsia is much benefited by the administration of hydrochloric acid.

Hydrochloric acid acts in the stomach not merely by activating the pepsinogen, but also as a powerful antiseptic influence, and thereby lessens fermentation. The quantities of hydrochloric acid ordinarily given as a digestant are ridiculously small. The most favorable acidity for gastric digestion is equivalent to about 0.2 per cent. of absolute hydrochloric acid; 10 minims of the official dilute hydrochloric acid mixed with one-half a tumblerful of water will make a solution representing between 0.05 and 0.1 per cent. of absolute hydrochloric acid. It is manifest, however, that in such doses it can have very little favorable influence upon the digestive processes. The proper dose of dilute hydrochloric acid should be not less than 30 minims. If an injurious effect upon the teeth is feared from the use of these acids they can be taken through a glass tube, or, better, the mouth rinsed immediately after taking them with an alkaline solution.

Nitro-hydrochloric acid is by many believed to exercise a beneficial effect upon the liver. If it is of value in so-called congestion of the liver and chronic hepatitis, for which there is considerable clinical evidence, its utility is more probably due to some reflex effect rather than any direct action upon the biliary secretion. It is also asserted that nitro-hydrochloric acid is a specific in that peculiar congery of symptoms which is characterized by a feeling of general malaise and depression of spirits and the presence of crystals of calcium oxalate in the urine.

Nitric acid, although capable of serving as a digestant, is less frequently employed for this purpose than hydrochloric acid. Its most common use in medicine is as a caustic for the destruction of warts and other small dermal growths. A drop or two may be applied by means of a glass rod, and, when the action has gone far enough, neutralized with sodium carbonate or soapsuds. Several applications are generally required. Sulphuric acid is by many supposed to have astringent properties, and is, therefore, used to a considerable extent in diarrhœa mixtures and even for the relief of night-sweats. It is also antidotal to lead, but is generally employed for this purpose in the form of a salt. The soluble sulphates are cathartic.

Hypophosphorous acid, and especially its salts, enjoy great popularity as tonics in the treatment of various conditions of malnutrition. The value of the compound syrup of hypophosphites, however, the form in which the remedy is most employed, depends rather upon the iron and strychnine and other bases which it contains than upon the hypophosphorous acid.

Toxicology.—Sulphuric, hydrochloric, nitric, and nitro-hydrochloric acids, when in concentrated form, rapidly destroy all organic tissues, and are, therefore, corrosives, hydrochloric acid being the feeblest.

Owing to its abstraction of the element of water from the carbon of organic tissues, sulphuric acid blackens organic matter at the same time that it destroys its texture; nitric acid stains organic tissue a deep yellow color; nitro-hydrochloric acid produces a somewhat similar but much less pronounced discoloration. In the detection of poisoning by one of these agents the color of the stain upon the person or clothing is often of great assistance. Holes made in the linen by one of these acids are to be distinguished from those made by fire or mechanical violence by the pulpy character and acid reaction of the edges.

The general symptoms of poisoning by mineral acids are similar, and depend for their severity especially upon the amount and the concentration of the dose taken, although sulphuric and nitric acids are more powerful than is hydrochloric acid. Death from collapse has resulted in two and a half hours, but months may be required in the working out of the fatal result. The symptoms are immediate pain in the mouth, gullet, and epigastrium, violent vomiting (after sulphuric acid the matters may be tarry), and rapid collapse marked by cold wet

surface, feeble pulse, and suppressed voice. The mind is usually clear until very late in the poisoning. The treatment of poisoning by a mineral acid consists in immediate neutralization of the acid by means of non-irritant alkali, such as magnesia, bicarbonate of soda, or soap, and then treating symptomatically.

PEPSIN.

As is well known, there is secreted by the gastric glands a peculiar albuminous body, which has the power not only of coagulating albumin, but also, with the aid of acidulated water, of redissolving it. To this principle the name of pepsin has long been given. A discussion of its nature and properties would be more in place in a work on physiology than in one on therapeutics.

Pure pepsin has never been isolated. The substance recognized by the Pharmacopœia under the name of pepsin is made by the auto-digestion of the mucous membrane of the pig's stomach and, after several days, separating the pepsin by the process of salting out. As thus obtained, it will contain, of course, a considerable and varying amount of other albuminous bodies. The United States Pharmacopœia makes as the standard of pepsin that it should be able to digest not less than three thousand times its weight of egg albumin in two and one-half hours at a temperature of 125.6° F., but much stronger pepsins have been prepared commercially.

Incompatibilities.—The digestive power of pepsin is destroyed by strong acids (more than 1 per cent. of HCl), by alkalies, by strong alcohol (more than 10 per cent.), by the soluble salts of the heavy metals, and by tannic acid. Pepsin and pancreatin are mutually incompatible, one or the other being destroyed, according as to whether the medium is acid in reaction or not.

Therapeutic Uses.—For reasons already pointed out, it is only in rare cases that pepsin is of any great value as an aid to digestion. If it is to be employed for this purpose, however, it should at least be given in doses which may prove of some service; at least one-half a drachm (2 grammes) of the ordinary commercial article should be exhibited at a dose. Although of minor importance as digestants, solutions of pepsin afford excellent vehicles for the administration of irritant drugs, such as the iodides, and apparently, also, are capable of relieving certain cases of vomiting due to irritation of the gastric mucosa. It is doubtful how far the first effect is due to anything more than mere proteid action.

PANCREATIN.

Pancreatin has been used to a considerable extent as a digestant and is recognized by the United States Pharmacopœia. It is highly improbable, however, that it can exercise any beneficial influence upon the digestive processes, as Sollmann has shown that a mixture of

one-tenth per cent. hydrochloric acid and pepsin completely destroys its digestive properties. Of the numerous concoctions which are largely exploited by their proprietors, and professed to contain both pancreatin and pepsin, it seems hardly necessary to speak, were it not for the fact that they are so widely employed in medicine. It is absolutely impossible that they can contain both of these active ferments, and it is probable that they contain neither.

Therapeutic Uses.—Pancreatin has been used in cases of digestive failure especially because it acts on the carbohydrate foods as well as on the proteids. It must be borne in mind that it is not active in the presence of free acid, and in the normal gastric juice is not only incapable of affecting digestion but will itself be digested. If used as an aid to digestion it should be given before meals and combined with a sodium bicarbonate.

The most important use for pancreatin is in the preparation of the so-called peptonized, or predigested, foods. It is greatly superior to pepsin for the purpose of predigesting foods, since the latter affects only the nitrogenous foodstuffs, while pancreatin acts also upon the starch and fats.

To make *peptonized milk* add 5 grains of pancreatin and 20 grains of sodium bicarbonate to a pint of milk, at a temperature of about 100° F. Digestion will be complete in one hour or one hour and a half. If the bitter taste which is developed is seriously objected to, the digestive action may be stopped at the end of a half hour by heating the milk almost to the boiling point.

To make *peptonized gruel* prepare a thick gruel with arrow-root, oatmeal, or other farinaceous article, add while still heated an equal quantity of milk, and when cooled to about 100° F. 5 grains of pancreatin and 20 grains of sodium bicarbonate to each pint of the mixture. Digest at blood heat for two hours. Raise to boiling point and then strain.

It must be remembered that most peptones have a distinctly bitter taste and therefore thoroughly digested foods are very unpalatable. The bitterness may be partly concealed by the addition of aromatic flavoring extracts, but more commonly it is the custom to arrest the process of digestion before it is complete.

BILE.

The U. S. Pharmacopœia recognizes, under the name of *Fel bovis,* the fresh bile of the ox; also *Extractum fellis bovis,* a dried alcoholic extract of ox-gall mixed with sufficient starch that one part of the extract is equivalent to 8 parts of fluid bile. This extract consists chiefly of the characteristic salts, sodium glycocholate and sodium taurocholate. These salts have the power of emulsifying fats, and are used to some extent in the arts as cleansing agents.

Physiological Action.—It is beyond the scope of a work of this nature to discuss the rôle of bile in the processes of digestion, but it is impossible to consider this substance as a therapeutic agent

without making some reference to its effects on the intestinal tract.

When administered by the mouth ox-gall is absorbed rapidly in the upper part of the small intestines and carried by the blood to the liver. When it enters the circulation, either through absorption from the intestinal canal or by injection directly into the blood-stream, it causes a marked increase in the secretion of bile by the liver. The question as to whether the amount of increase in the formation of bile is greater than that which is represented by the quantity introduced into the circulation is as yet unsettled, but it is probable that the biliary salts are directly stimulant to the secreting cells of the liver.

Besides aiding in the digestion of fats the presence of bile in the intestinal tract is important because of its effects upon the peristalsis. According to Scheepbach the bile salts inhibit the movements of the small intestines but increase those of the larger bowel.

When injected intravenously in large quantities bile causes a fall in blood-pressure with slowing of the pulse. The experimental evidence is contradictory as to whether this slowing of the pulse is an evidence of increased cardio-inhibition or not, but it seems well established that this drug is a direct depressant to the cardiac muscle. It also lessens the contractility of other muscle tissues when in direct contact with them.

According to Fraser, bile, probably by virtue of the cholesterin in it, has the power of detoxicating snake venom and certain bacterial toxins. Bile has distinct antiseptic properties, and, according to Loehlein, the bile salts possess bacteriolytic powers especially towards the gonococci.

Therapeutic Uses.—Purified ox-gall is used in medicine to replace the natural bile when absent from the intestinal tract. It may be pointed out, however, that where the absence of bile in the intestines is due to mechanical obstruction in the bile passages, for instance when a stone is lodged in the common duct, the administration of this remedy by the mouth cannot exercise any influence upon the digestive organs beyond the upper part of the duodenum, because of its rapid absorption. When, however, the condition is due to sluggishness of the secreting cells of the liver it may be of much value.

Bile is often of value in the treatment of chronic constipation. Its benefit here is due in part to its stimulant influence upon peristalsis of the colon, and in part to the fact that in some manner not completely understood it enhances the action of certain of the vegetable cathartics, notably podophyllum, jalap, rhubarb and senna.

The other uses to which bile has been put are yet in the experimental stage. Loehlein recommends it in the treatment of ophthalmia neonatorum; he asserts that sodium glycocholate not only possesses gonicidal properties itself but by virtue of its solvent action on mucus and pus renders possible more perfect cleansing of the eye so that the silver salts are capable of being brought into intimate contact with the infecting micro-organisms. Almagia and Mendes recommend it in the treatment of tetanus on the grounds that it has the power of neutralizing the toxin.

BILE.

Almagia and Mendes.....il Morgagni, 1907.
Fraser.....B.M.J., 1897, ii, p. 125, and 1898, ii, p. 627.
Loehlin.....D.M.Ztg., 1909.
Meltzer and Salant.....J.Ex.M., 1907, vii and viii.
Ott and Scott.....T.G., 1909.
Richardson.....T.G., 1906.
Schaeffer.....A.J.P., xvii, p. 362.

MALT.

There are a number of ferments of vegetable origin which are capable of converting starches into sugar and some which are capable of converting albumins into albumoses. The superiority of the latter, however, over pepsin is not clear, and it is doubtful if they are of any value in medicine. It is probable, however, that certain cases of starchy indigestion may be benefited by the use of vegetable enzymes. The most important of these is the ferment *diastase* which is formed during the germination of the seeds of barley and other grains. The substance known as malt is the seeds of the barley which have been caused to enter the incipient stage of germination and dried. It is prepared by soaking the grains in water and leaving them germinate at a moderate temperature and then drying and killing the germ by heat. If the temperature be raised to a point high enough to scorch the grain the malt is of a dark color. As thus prepared malt will contain dextrine and glucose and other nutritive substances, besides the starch-digesting ferment diastase and also a second soluble ferment, known as peptase, which is capable of changing proteins into peptones. The official extract of malt is made by macerating malt with water for a number of hours and then evaporating at low temperature to the consistency of thick honey. It is a highly nutritive preparation and also possessed of some digestive power, and is valuable as an aid to nutrition in many conditions of cachexia. It also is of service as an emulsifying agent.

Under the name of malt extract is often sold a liquor which differs but very slightly in its composition from beer. It has but very little of the therapeutic virtue of the real extract of malt.

ALKALIES.

The alkalies, as such, are used either to neutralize excessive acidity in the alimentary tract or to correct reduced alkalinity in the other body fluids. When used for their effects in the digestive system they are generally spoken of as antacids.

Excessive acidity in the stomach may result from an abnormal activity of the acid glands (hyperchlorhydria) or from fermentation of starchy and fatty foods with the formation of organic acids. In either instance there will be gastric uneasiness, sometimes amounting to distinct pain, in the epigastrium and the rising of a sour fluid into the mouth, and oftentimes headache accompanied with nausea. The

diagnosis between the two forms can often be made only through an analysis of the gastric contents, but, generally speaking, the symptoms of hyperchlorhydria disappear to a large extent after eating, on account of the formation of acid albumins, which are less irritant than is the free acid. It is commonly believed that hyperchlorhydria may be a precedent to gastric ulcer, and certainly in this condition we usually find the stomach contents highly acid. Neutralizing the excessive acidity not only lessens the sense of discomfort but also tends to encourage the healing of the underlying condition, for in the case of the hyperchlorhydria the low-grade irritation of the stomach acts as an excitant upon the glands of the stomach, increasing their functional activity, and consequently the condition is self-perpetuating to a considerable extent. On the other hand, some of the organic acids are sufficiently irritant that they give rise to an inflammation of sufficient severity to carry the gastric glands beyond the stage of increased activity to one where the secretion is in abeyance, and the correction of the excessive acidity in the second instance also tends to cut short the disease. The intestinal tract, at least below the duodenum, is normally alkaline rather than acid, but in conditions of acute inflammation may become highly acid, due to fermentative changes. This condition is seen most frequently in infants, and is found associated with a diarrhœa in which the passages have a green color and hence are sometimes spoken of as spinach stools. In diarrhœas of this character, as well as in colic, antacids are often of service by overcoming the acidity in the intestinal canal. It was formerly believed that the introduction of alkalies into the stomach led to heightened activity of the acid glands, but present evidence seems to show that this increased secretion of hydrochloric acid is only to the point necessary to neutralize the alkali administered.

Various substances which have already been discussed in this work are excellent antacids, most of them uniting this to other medicinal properties. Thus, when a stimulating antacid is desired, as is very often the case in sick headache, half a drachm of the aromatic spirit of ammonia may be taken, well diluted with water. Potassium and its carbonates have already been dwelt upon with sufficient detail. They may be used as antacids; but, as they exert other powerful influences upon the system, they are, we think, not so generally useful as the soda preparations.

While the system has so many methods of preserving its alkalinity that the reaction of the blood is not altered except in the gravest forms of metabolic disturbances, yet it is not improbable that that group of diatheses known variously as lithæmia, chronic gout, etc., are attended with an increased formation of acid substances. At least, in many of these cases we find the urine highly acid, and the attempt to correct the excessive acidity or diminished alkalinity with the use of alkalies would seem a rational procedure. It is impossible, however, to administer sufficient quantities of alkalies by the stomach to seriously influence the acidity of the whole body without risk of unduly disturbing

digestion. There are, however, certain salts, especially the citrates, which, while themselves practically neutral in reaction, are oxidized in the stomach and appear in the excretions in the form of alkaline carbonates, and these are generally given the preference where it is desired to correct systemic rather than local acidity. These are considered elsewhere (see page 29).

The alkaline salts considered in this chapter are those of sodium, magnesium, and calcium.

SODIUM.

Materia Medica.—The official salts of sodium which are useful for their antacid effects are the hydroxide, the carbonate, and the sodium hydrogen carbonate, commonly known as the bicarbonate.

Sodium hydroxide is usually found in the form of white or nearly white sticks or pencils which deliquesce and subsequently absorb carbonic acid.

Sodium carbonate is found commercially united with various proportions of water of crystallization. The Pharmacopœia recognizes only the monohydrated sodium carbonate; this is a white, crystalline, granular powder without odor but with a strongly alkaline taste. It is soluble in 2.9 parts of water and insoluble in alcohol.

Sodium bicarbonate is a white, odorless powder with a mildly alkaline taste, soluble in 12 parts of water at 59° F. At higher temperatures it gradually loses carbonic acid and is changed into a carbonate. It gives a slightly alkaline reaction with litmus.

Official Preparations:

Sodii Hydroxidum [Caustic Soda]	Not used internally
Liquor Sodii Hydroxidi (5 per cent.)	15 minims (1 mil).
Sodii Carbonas Monohydras [Washing Soda]	5 to 10 grains (0.3–0.6 Gm.).
Sodii Bicarbonas [Baking Soda]	10 to 20 grains (0.6–1.2 Gm.).
Sodii Citras	15 to 30 grains (1–2 Gm.).

Therapeutic Uses.—The sodium ion has the least influence upon the functions of the body of any of the earthy metals, and its alkaline salts are, therefore, the remedies of choice where we simply desire to correct hyperacidity in the intestinal tract. Ordinarily the bicarbonate is to be preferred as being the least irritant of these salts. In conditions of true acidæmia, such as is seen in the advanced stages of diabetes, in which it is necessary to make a profound impression on the alkalies, bicarbonate of soda may be injected intravenously. For this purpose a 1.8 per cent. solution should be employed as being practically isotonic with the blood; of such a solution one quart may be injected at a dose with due precautions as to asepsis.

The sodium hydroxide, like other soluble hydroxides, is caustic in its action, and is very rarely employed internally. As an escharotic it is a very powerful agent of great penetration, whose chief drawbacks are its painfulness and the difficulty of its control. It appears to act chiefly by abstracting water and, to some extent, by a solvent action upon the tissues, especially the fat. It is used where a very deep and

decided influence is required, as after the bite of a rabid animal. The best method of application is as follows: Take a piece of thick adhesive plaster, and cut a hole in it of such size that, when the piece is warmed and properly placed upon the skin, the part to be acted upon will be exposed, while all around it will be protected. Then apply the plaster, and grease the outer surface of it, without allowing any of the oil to come in contact with the exposed central skin. Then lay the caustic potash upon the latter, and, when the action is believed to have extended deep enough, wash the part with dilute vinegar.

MAGNESIUM.

Of the alkaline salts of magnesium there are official two forms of the oxide and the carbonate. The oxide of magnesium is manufactured by the action of heat upon the carbonate, and is therefore spoken of as calcined magnesia.

The *heavy* and the *light* magnesia differ only in their physical characters, the particles being differently aggregated. Magnesium carbonate is manufactured by precipitating a solution of magnesium sulphate by one of sodium carbonate. If the two solutions be concentrated, the dense or heavy carbonate will fall; on the other hand, if the solutions be dilute, the precipitate will be a light carbonate. Heavy magnesia is obtained by calcining a heavy carbonate; light magnesia, by using a light carbonate. All of these substances are of a milk-white color, and occur in powder; the carbonates sometimes in very light cubical blocks. They are all practically insoluble in water, freely soluble in dilute acid, and in the presence of acids they will act as alkalies.

Official Preparations:

Magnesii Oxidum [Calcined Magnesia] .....1 to 4 drachms (4–15 Gm.).
Magnesii Oxidum Ponderosum .....1 to 4 drachms (4–15 Gm.).
Magnesii Carbonas .....1 to 4 drachms (4–15 Gm.).

Therapeutics.—The general effects and uses of magnesium have already been described (see page 272). The magnesium ion is so slowly excreted from the intestinal tract that when given by the mouth not only does it fail to exercise any of its influence upon the general system, but its soluble salts act as laxatives. Although both the carbonate and oxide are insoluble under ordinary circumstances, they are converted into soluble salts by the acids in the upper part of the alimentary canal, and, therefore, are not only antacid but also laxative in their effects. They are much used in hyperacidity of the alimentary tract, especially when some laxative action is desired. If they fail to produce the desired laxative action they should be followed with some acid drink, as lemonade.

Under the name of *Magma magnesiæ* the National Formulary recognizes a suspension of magnesium hydroxide in water. One flui-

drachm of this preparation, popularly called "milk of magnesia," represents three grains of magnesia hydroxide. It is widely used as a mouth wash.

CALCIUM.

Of the numerous salts of calcium there are considered here only those in which the action of the basic ion predominates. These are the oxide, the carbonate, and the chloride.

Calcium oxide, or lime, is made by calcining the carbonate, and occurs as white or grayish-white masses which when exposed to the air absorb carbonic acid and crumble to a white powder. When moistened with about one-half its weight of water there is formed, with the evolution of much heat, a white powder, calcium hydroxide or slaked lime. Lime is soluble in 760 parts of water at 77° F., but becomes less soluble as the temperature of the water is raised, so that boiling water will dissolve but one part in 1,600.

Calcium carbonate is a very wide-spread natural salt, being the basis of marble, chalk, and Iceland spar. The United States Pharmacopœia recognizes two forms of calcium carbonate, namely, prepared chalk and the precipitated calcium carbonate. Each of these occurs as a white powder practically insoluble in water, although small quantities may be dissolved in solutions of carbonic acid.

Calcium chloride is seen in the form of white, semi-translucent fragments, odorless, but with a sharp saline taste. It is soluble in 1.3 parts of water and 8 parts of alcohol, and is extremely deliquescent.

Calcium lactate occurs in white, granular masses or as a powder. It is soluble in 20 parts of water.

Calcium hypophosphite is odorless, but has a disagreeable bitter taste and is freely soluble in water.

Official Preparations:

Calx [Calcium Oxide: Lime]	Not used internally.
Liquor Calcis [Lime Water] (0.14 per cent.)	1 to 4 fluidrachms (4–15 mils).
Syrupus Calcis (6.5 per cent.)	10 to 20 minims (0.6–1.2 mils).
Linimentum Calcis [Carron Oil]	External use.
Calcii Carbonas Præcipitatus	15 to 60 grains (1–4 Gm.).
Creta Præparata [Prepared Chalk]	15 to 60 grains (1–4 Gm.).
Pulvis Cretæ Compositus (30 per cent.)	½ to 1 drachm (2–4 Gm.).
Mistura Cretæ (6 per cent.)	½ to 1 fluidounce (15–30 mils).
Calcii Chloridum	10 to 20 grains (0.6–1.2 Gm.).
Calcii Lactas	10 to 20 grains (0.6–1.2 Gm.).
Calcii Hypophosphis	10 to 20 grains (0.6–1.2 Gm.).

Physiological Action.—While sodium is the most abundant inorganic element in the system the presence of certain other earthy metals is essential to life. As was shown many years ago by Ringer, it is essential for the maintenance of the cardiac activity that there should be a certain ratio between the amount of sodium and calcium in the nutrient solution, and any serious disturbance of this balance between these two elements leads to disturbance of the cardiac action.

More recently it has been shown that the other tissues of the body are at least equally sensitive to disturbances in the amount of calcium and sodium in the blood. Thus, the intravenous injection of considerable doses of lime salts lessens the irritability of the cerebral cortex (MacCallum and Voegtlin) and the diminution in the proportion of calcium in the circulating fluid leads to an increased irritability of the cerebrum, and also to muscular twitchings.

The importance of lime in these conditions seems to be to neutralize some toxic effect of the sodium, so that an excess of either element is likely to lead to a disturbance of the normal functions. It is, however, impossible to introduce a poisonous amount of lime into the circulation through the alimentary canal, because the elimination will keep pace with the absorption. (Compare with potassium, page 31.) On the other hand, when there is a deficiency of lime in the food supply, or probably what is more important, a disturbance in the calcium metabolism, there is reason to believe that serious symptoms may be produced, which are generally regarded as symptoms of lime starvation, but which might more properly be considered as symptoms of sodium poisoning.

Lime also seems to be necessary for the activity of certain ferments. Thus, rennet does not coagulate milk in the complete absence of lime salts, nor does clotting take place in decalcified blood. An excess of lime, at least within certain limits, apparently hastens the coagulability of the blood.

The demonstration of the evil results following a reduction in the proportion of lime has led to the theory that certain diseased conditions are due to the absence of this element, and consequently to the use of lime as a corrective agent. One of the earliest applications of this thought was in the treatment of various diseases of the bones, notably in rickets, but there is very rarely any serious deficiency of lime in the food, and the effects of the oral administration of calcium salts in cases of rickets has not produced any very marked results. MacCallum and Voegtlin have more recently brought forward the theory that certain convulsive disorders, such as tetany, are the result of a diminution in the amount of calcium in the blood, and the soluble salts of the element have been used clinically with apparent success in this condition, as well as in other spasmodic disorders.

The salts of lime also seem to increase the resistance of the red blood-cells to certain hæmolytic serums, and also to lessen the liability of anaphylactic reaction in sensitive animals. For one, or both of these reasons, it has been found clinically to control the so-called "serum disease," that is, the febrile condition which sometimes follows the use of diphtheria antitoxin. Evidence has also recently been brought forward that it will counteract such conditions as hay-fever and asthma, which appear in some way to be pathogenically allied to anaphylaxis.

Concerning the effects of the internal administration of calcium salts upon the coagulability of the blood, and the consequent usefulness in hemorrhagic conditions, there has waged for years a vigorous dis-

pute. The present evidence is so contradictory that one is not justified in drawing too positive conclusions as to the effects of calcium in internal hemorrhages, but the weight of testimony seems rather to favor the view that, in some cases at least, it has exercised a favorable action. At least the treatment has the merit of being harmless, and in the face of our helplessness in hæmoptysis, and in intestinal hemorrhages, the clinician may well be justified in at least giving it a trial.

The alkaline salts of calcium are used especially in the treatment of diarrhœas with acid discharges. Some justification for this popular employment is found in the experiments of MacCallum, who finds that calcium salts inhibit peristalsis. The saturated solution of calcium hydroxide commonly known as lime water is used to a considerable extent for the purpose of increasing the digestibility of the milk. The addition of one or two tablespoonfuls of lime water to a glass of milk prevents the formation of large solid curds which are relatively indigestible. This effect is probably the result of the alkalinity. Lime water is also used externally in a variety of skin diseases, and its mixture with olive oil was at one time a very popular treatment for burns, under the term of Carron oil (so called from the name of the iron works at which its reputation was first made). It is being rapidly replaced, however, by applications more in keeping with the principles of modern aseptic surgery. Powdered chalk is sometimes employed as a desiccant powder. Its action for this purpose is purely mechanical, and generally the powdered talc is preferable to the chalk.

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MacCallum and Voegtlin ....J. Ex. M., 1909, xi, 118.
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CHARCOAL.

Charcoal (*carbo ligni*) is made by partially burning wood. This is accomplished either by regulating the access of air during the process of combustion or by heating the wood in iron cylinders. The best quality of charcoal is obtained from willow twigs. It occurs in black, highly glistening, brittle pieces or as a powder, odorless and tasteless, insoluble in the ordinary solvents. It has a remarkable power of absorbing gases, being capable of taking up ninety times its volume of ammonia, fifty-five times its volume of hydrogen sulphide, and thirty-five times its volume of carbon dioxide.

Therapeutics.—The chief use of charcoal in medicine is in the treatment of gastric indigestion, especially when there is much fermentation and formation of gas. It was originally employed with the idea of absorbing the gas in the stomach and thus lessening distention;

it appears, however, to have some other beneficial effect, perhaps acting mechanically, by protecting the gastric mucous membrane against the irritant effects of fermentation. The dose is 15 to 30 grains (1–2 Gm.).

Charcoal is also employed by surgeons to absorb the malodorous gases given off in gangrene or foul ulcers. It has long been known that charcoal is capable of absorbing alkaloids, and it has been used as an antidote in various forms of poisoning, and Kraus and Barbara (W. K. W., 1915, xxviii) assert that it has the power of absorbing bacterial toxins and it is a useful drug in the treatment of dysentery.

FULLER'S EARTH.

Various forms of clay are used in medicine for their mechanical properties. Under the name of "kaolin" the U. S. Pharmacopœia VIII recognized the sort known as porcelain clay, but in the present Pharmacopœia this has been replaced by the diatomaceous earth commonly known as fuller's earth—from its use in fulling cloth—or by its German name, *kieselguhr;* the official title is *Terra silicea purificata.* These clays are mixtures of silica and alumina; according to Hess, fuller's earth consists of 57.26 per cent. of silicum oxide and 18. 33 per cent. of aluminum oxide, with traces of iron, calcium, and magnesium oxides, and 18 per cent. of water. The Pharmacopœia provides, however, that the earth shall not contain more than 10 per cent. of moisture. Siliceous earth is a bulky impalpable powder, white or of a pale grayish color, without odor or taste. It readily absorbs water and other fluids, and has the power of removing many poisons from their aqueous solutions. This action appears to be due to the formation of colloidal compounds, and the process is spoken of as adsorption.

Clay is used in medicine for a variety of purposes besides its pharmaceutical uses. Mixed with glycerine and water, it is used as a conveyor of heat instead of the flaxseed poultice, but appears to be inferior. Fantus has shown that it is a valuable antidote in the treatment of morphine poisoning, and presumably of value in some other alkaloidal intoxications. Hektoen and Rappaport state that the dry powder blown into the nose removes all bacteria and is a useful measure in the treatment of diphtheria carriers. Fuller's earth apparently also has the power of adsorbing bacterial toxins, and has been used to a considerable extent in the treatment of various forms of enteritis, both in children and adults, and even in Asiatic cholera. Its value in this condition appears to be due in part to its mechanical protective effect and in part to the adsorption of the irritant secretions and bacterial products in the intestinal canal. It is also used as a local application to suppurating wounds and purulent catarrhs, in which conditions it not merely absorbs the pus but appears to exercise a restraining influence on bacterial growth. In enteritis or gastritis siliceous earth may be given in doses of 2 or 3 ounces suspended in water and flavored to taste.

FULLER'S EARTH.

Fantus ..... J.A.M.A., 1915, lxiv, p. 1838.
Hess ..... J.A.M.A., 1916, lxvi, p. 106.
Rappaport ..... J.A.M.A., 1916, lxvi, 943.
Stumpf ..... M.M.W., 1898; 1911; 1914.
Zweifel ..... M.M.W., 1910, p. 1787.

DEMULCENTS.

These are bland substances, which form more or less gummy or mucilaginous solutions in water, capable of exerting a calming or soothing influence upon inflamed surfaces. Their action is probably purely mechanical, their adhesiveness causing the water they are in to remain long upon the part; they are, as it were, vehicles for water, the demulcent *par excellence*. It has been affirmed that demulcents taken internally relieve irritation in distant organs. There is, however, no reason for supposing that such of them as escape digestion are absorbed or yield to absorption any principles in sufficient quantity to exert an influence upon the general system. The relief which undoubtedly follows their use in certain affections of parts which they can reach only through the circulation is probably due to the large quantities of water with which they are administered.

Clinically, demulcents are useful as local applications in all forms of acutely inflamed surfaces, and they are taken internally in acute inflammatory conditions of the alimentary canal. In slight bronchial irritation they are often of service, especially when allowed to dissolve slowly in the mouth: used in this manner, they not only exert an influence upon the mucous membrane of the mouth, but very probably find their way also into the respiratory passages.

Acacia.—*Gum arabic* is a gummy exudation from *Acacia senegal,* and other species of acacia, small trees growing in Northern Africa, Cape Colony, and Australia. Gum arabic occurs in roundish pieces, more or less transparent, brittle, varying in color from white or yellowish-white to amber. It consists of a feebly acid, amorphous principle, *arabin,* united with lime, potassium, and magnesium oxide. In the plant, arabin, like other gums, appears to be formed by a retrograde metamorphosis of cellulose.

On account of its solubility in water and pleasant taste, gum arabic is often used as a demulcent in irritation of the fauces and in angina. Its chief medical use, however, is in the making of emulsions, pills, etc. The mucilage (*Mucilago acaciæ*) is official.

Tragacantha.—*Tragacanth* is the concrete juice of *Astragalus gummifer,* and of other species of astragalus, a small shrub of Asia Minor. Tragacanth occurs in large, whitish, horny, waved flakes. Introduced into water, it does not dissolve, but swells up into a soft paste. It contains, beside arabin, *Bassorin,* a gummy principle, at once distin-

guished from arabin by its not dissolving in water, but simply swelling up into a pasty mass. Tragacanth is used only in the manufacture of troches and in suspending heavy powders, for which purpose the difficulty of its solution and the extreme viscidity of its mucilage especially fit it. Its mucilage (MUCILAGO TRAGACANTHÆ, U. S.) is official.

ULMUS.—*Slippery Elm* is the inner bark of *Ulmus fulva,* a large indigenous tree. The bark is of a yellowish-white or tan color, fibrous, yet when dry somewhat brittle, and occurs in long, flat strips or pieces one or two lines thick. It is pleasantly mucilaginous when chewed. It contains a large quantity of a peculiar mucilage, which yields freely to water. Its infusion is sometimes taken in large quantities in inflammations of the intestines, as a demulcent laxative. When ground into powder, slippery elm makes an excellent soothing poultice.

CHONDRUS.—*Irish Moss,* or *Carrageen.*—The fronds of *Chondrus crispus* and of *Gigartina mamillosa,* sea-weeds growing on the coast of Ireland, and also on the northern coast of the United States, where they are now gathered in large quantities. The fronds are purplish-red—but, as kept in the shops, bleached by washing in fresh water, whitish and translucent—cartilaginous, slender, much branched, swelling up but not dissolving in water, and having a slightly saline taste. Their virtue depends chiefly upon a starch- or gum-like principle, *carrageenin,* which is distinguished from starch by not turning blue with iodine, and from gum by not precipitating from its watery solution on the addition of alcohol. Chondrus also contains a notable proportion of a vegetable albumin.

Carrageen, being demulcent and nutritious, is employed as an article of diet in those cases requiring food of such character, and may be used instead of arrow-root. It is to be prepared by first soaking for ten minutes in cold water, and then boiling from half an ounce to an ounce of it (according to the desired consistency) in a pint and a half of water down to a pint, sweetening and flavoring to taste. Milk may be substituted for water.

GLYCYRRHIZA.—*Licorice root* is the root of *Glycyrrhiza glabra* and *glandulifera,* native herbs of Southern Europe. It occurs in long, cylindrical pieces, from a few lines to more than an inch in diameter, brownish externally and yellowish within. Its fracture is fibrous, its taste sweet and mucilaginous, its odor none. It is used almost exclusively in the form of the extract, known as licorice. Its active principle is *glycyrrhizin.* This is a sweet, neutral substance, differing from the sugars in not being converted by nitric acid into oxalic acid, and by its inability to undergo the vinous fermentation.

Licorice is very largely used as a demulcent in pectoral complaints, and, on account of its pleasant taste, as a means of disguising or of flavoring medicines. In the form of glycyrrhizin it is said to conceal almost entirely the bitter taste of quinine and similar substances. The compound mixture of glycyrrhiza is much used as a domestic remedy in colds and the early stages of mild bronchitis. The

ammoniated glycyrrhizin is an elegant demulcent preparation which, however, is incompatible with acid or alkaline solutions.

Linseed or flaxseed is the seed of *Linum usitatissimum,* or common flax, and contains large quantities of mucilage and of oil; its infusion, *Flaxseed tea,* is much used internally. It is often made with boiling water; but the application of too much heat causes the extraction of the oil, and renders the preparation less palatable. The addition of lemon and sugar makes it more palatable. It may be drunk *ad libitum* in pectoral catarrhs, in enteritis and dysentery, and in irritation of the kidneys or the urinary passages.

Starch.—Obtained from Indian corn, a white, inodorous, tasteless powder, composed of microscopic granules, is physiologically inert except as a food. It is often used as a dusting powder in irritant conditions of the skin; as a soothing demulcent in the preparation of opiates and other rectal injections, and pharmaceutically for the purpose of thickening or gelatinizing ointments, and the making of paste for use in skin diseases. The official glycerite (*Glyceritum Amyli*) is a translucent jelly of ointment-like consistency.

EMOLLIENTS.

True emollients are perfectly bland, fatty substances, which, when applied to the skin, soften it and render it more pliable. The action of these remedies is largely mechanical, and they probably soften the derm in precisely the same way as they affect a raw hide or a piece of leather. They are therefore especially useful when the skin has a tendency to crack or to chap. Whenever surfaces become sore by attrition, or, in other words, chafe, emollients are also useful mechanically. They often afford relief in simple inflammations of the skin under such circumstances that their action cannot be explained as purely mechanical: indeed, they seem to exert a dynamic influence upon the nutrition of the parts concerned. It may be that they shut out or interfere with the development of pathogenetic germs, or, in other words, that they are mechanical antiseptics. Be these things as they may, clinical experience has demonstrated that fatty matters are of very great value in the treatment of superficial inflammations. The blandest fat, when it becomes rancid, is irritating, and will do more harm than good, so that the strictest attention must be paid to the condition of the fatty material employed. Any perfectly bland oily substance may be used as an emollient.

The fatty bases are also used as a means of introducing drugs into the system through the skin. Thus the so-called endemic method of administering remedies is used, especially for substances which are likely to irritate the alimentary tract. The disadvantages of this channel of absorption are its slowness and uncertainty of dosage. There does not appear to be any marked difference in the power of true fats in penetrating the skin except in so far that a hard fat does not melt readily at the temperature of the body and, therefore, does not yield

itself to absorption as readily as a soft one. The petrolatums, however, are not at all fitted for ointment bases when systemic effects are desired.

The true fats are combinations of oleic, palmitic, stearic, or allied acid with glycerol. Most fats contain more than one of the fatty acids. The consistence depends on the relative proportion of the various fatty acids: the most fluid of the ordinary fats is olein and the most solid is palmitin, stearin occupying a midway position.

There are certain substances, as petrolatum and glycerol, which, while not fats in the proper sense of the word, have similar emollient virtues and are, therefore, considered in this family.

The fixed oils and true fats are insoluble in water and, with the exception of castor oil, only sparingly soluble in alcohol. When brought in contact with alkalies their fatty acid unites with the alkali to form a soap, glycerine being liberated. Both oleic acid and stearic acid are also recognized by the Pharmacopœia, the former being a yellowish oily liquid which is soluble in alcohol, chloroform, and benzene, but insoluble in water. Stearic acid is a solid which dissolves in 16.6 parts of alcohol.

Official Fats and Ointment Bases:

Official name.	Common name.	Consistency.	Congealing or melting point.
Acidum Oleicum	Oleic Acid	Liquid	39.2° F.
Acidum Stearicum	Stearic Acid	Solid	133°–156° F.
Adeps	Lard	Soft	100.4°–104° F.
Adeps Benzoinatus	Benzoinated Lard	Soft	
Adeps Lanæ	Wool-fat	Soft	104° F.
Adeps Lanæ Hydrosus	Lanolin	Soft	104° F.
Cetaceum	Spermaceti	Solid	113°–122° F.
Sevum Præparatum	Mutton-suet	Solid	113°–122° F.
Cera Alba	White Beeswax	Solid	147°–149° F.
Cera Flava	Yellow Beeswax	Solid	144°–147° F.
Oleum Adipis	Lard Oil	Liquid	32° F.
Oleum Amygdalæ Expressum	Oil of Sweet Almond	Liquid	−4° F.
Oleum Gossypii Seminis	Cotton-seed Oil	Liquid	23°–32° F.
Oleum Lini	Linseed Oil	Liquid	−4° F.
Oleum Olivæ	Olive Oil	Liquid	32° F
Oleum Ricini	Castor Oil	Liquid	0° F.
Oleum Theobromatis	Cocoa-butter	Solid	86°–95° F.
Glycerinum	Glycerine, Glycerol	Liquid	
Paraffinum	Paraffin	Solid	125°–135° F.
Petrolatum	Vaseline	Soft	113°–118° F.
Petrolatum Album	White Vaseline	Soft	113°–118° F.
Petrolatum Liquidum	Albolene	Liquid	

Official Mixed Ointment Bases:

Ceratum ..... White Wax 30, White Petrolatum 20, Benzoinated Lard 50 per cent.

Unguentum ..... White Wax 20, Benzoinated Lard 80 per cent.

Unguentum Aquæ Rosæ..... Spermaceti 12.5, White Wax 12, Expressed Oil of Almond 56, Sodium Borate 0.5, Stronger Rose Water 19 per cent.

Glyceritum Amyli ..... Starch 10, Water 10, Glycerine 80 per cent.

Olive oil is the ordinary salad oil of the table, and may be used wherever a very bland oil is desired. It has, however, no superiority for ordinary purposes over the *cotton-seed oil;* indeed, a very large proportion of the "sweet oil" of commerce is cotton-seed oil. Until comparatively recently much of the olive oil exported from the Mediterranean ports was highly adulterated, but since the passage of the "Food and Drug Act" this fraudulent traffic has almost ceased. There seems to be no sufficient reason for believing that olive oil differs from cotton-seed oil in its physiological or therapeutic properties. These oils are sometimes used internally with advantage, for nutritive purposes, and are also very mildly laxative. Olive oil has been used to a large extent for the relief of gall-stones, but since fats are absorbed chiefly, if not entirely, through the thoracic duct, it would appear that the oil must pass through the pulmonary circulation before reaching the liver. If olive oil has the asserted remedial influence, it probably acts reflexly through the nervous system—through a mechanism provided by Nature for the purpose of aiding in the digestion of fats when in excess. The dose of the oil should be not less than from five to seven fluidounces (150 to 215 mils), taken in four to eight portions in not longer than three hours. It may be given in aromatized emulsion, with a little brandy or whiskey if desired.

Oil of Theobroma, on account of its firm consistency and comparatively low melting point, is largely used for making suppositories and bougies.

Wool-Fat is obtained from the wool of sheep, which is said to contain, on an average, forty-five per cent. of it. It appears to be practically the same as the natural oil of the hair in man and other animals. The Hydrous Wool-Fat contains about thirty per cent. of water, and is the form of the unguent ordinarily employed. It was first recommended by Oscar Liebreich as a basis for ointments or preparations to be applied to the surface of the skin. It is entirely free from irritant properties, has the power of taking up a large amount of water without losing its unctuousness, and does not easily become rancid; it has been asserted that it is absorbed through the skin much more readily than are other fats. The experimental evidence on this point is contradictory, but the facts that lanolin is largely the secretion of sebaceous follicles, contains an abundance of cholesterin, and is in the nature of a waste product which is intended, not for absorption but for the keeping soft of the skin and its appendages, indicate very strongly that it will yield itself, and medicinal substances with which it may be impregnated, *less* readily to absorption than do other fats. As a basis of ointments used to medicate the skin it is most effective, but when absorption is desired it is probably inferior as a vehicle to ordinary fats.

GLYCEROL—GLYCERIN.

Materia Medica.—This is a thick, syrupy liquid, colorless, free from odor, and of a sweet taste. Chemically speaking, it is *propenyl*

alcohol. It is always set free during the process of saponification, and formerly was a by-product in the manufacture of soaps. At present it is made by the direct decomposition of fats by superheated steam.

Under certain circumstances, not well understood, glycerine forms hard, brilliant crystals. In its usual liquid form it mixes in all proportions with water and alcohol, and itself dissolves iodine, bromine, the alkalies, tannic and other vegetable acids, a large number of neutral salts, salicin, and other organic principles. It throws, however, most alkaloidal salts out of their watery solution.

Glycerine does not evaporate upon exposure, but is very hygroscopic, and absorbs water from the air. When pure, it is incapable of becoming rancid or of fermenting spontaneously. The acrid glycerine owes its irritant properties to impurities, especially to oxalic and formic acids; cheap grades of glycerine are frequently contaminated with arsenic.

Physiological Action.—When large doses of glycerine (in the dog eight or more parts per thousand by weight) are injected subcutaneously, death is produced in a period varying, according to the dose, from one hour to several days. The symptoms are loss of muscular strength, lethargy, bloody urine, vomiting, dryness of the mucous membrane, with marked thirst, fall of temperature, gradual extinction of both respiration and circulation, and finally convulsions and coma. After death intense congestion, with more or less softening of the tissue, is found in the lungs, kidneys, and intestines.

Catillon asserts that glycerine administered in small continuous doses exerts a decided effect upon nutrition, but the general drift of the present evidence is to show that glycerine has no distinct effect upon tissue-changes. When administered freely, however, it is absorbed from the alimentary canal and appears to be eliminated partly unchanged, but a proportion of it is oxidized in the body and apparently furnished energy to the system and thereby is capable of taking the place of a bodily fat.*

Very interesting in connection with the use of glycerine in diabetes is the assertion of Fuchsinger, that in rabbits slightly poisoned with glycerine no sugar appears in the urine after the "diabetic puncture." The experiments of Eckhard gave, however, a contrary result, and Catillon affirms that given in very large continuous doses glycerine increases the amount of sugar in the blood.

Therapeutics.—Locally applied, glycerine is usually unirritating, and it is much employed as an emollient. The chief disadvantage that attends its use is its stickiness; on the other hand, its non-volatility and its hygroscopic properties give a persistency to its action which is often very advantageous. It enters largely into the composition of popular emollient ointments, or "creams," as they are called, and is often used itself for chapped hands, excoriations, and similar troubles.

* For discussion of its effects on nutrition, see *Archiv f. d. Ges. Phys.*, 1889–90, xlvi.

It is also employed by dermatologists to some extent in chronic eczema; in seborrhœa, whether affecting the hairy scalp or other parts, it is asserted to be especially useful, softening the masses of secretion, and, used in conjunction with such remedies as borax, zinc, and lead acetate, diminishing the amount of secretion. Upon the mucous membranes glycerine acts very much as it does upon the skin, and diluted with water is very useful in coryza, and even, by enemata, in dysentery. It also forms an excellent basis for mouth washes; or a paste may be made with it and borax, or similar substance, for use in ulcerations of the same cavity. The list of diseases in which this remedy is employed might be very much lengthened; but the examples already given are sufficient to indicate the range of its application as an emollient and as a vehicle. There are certain persons upon whose skin and mucous membranes even the purest glycerine seems to act as an irritant. This influence is most intense when the glycerine is nearly or entirely free from water. It is, however, discernible even when the remedy is much diluted, and often inhibits its use. The existence of this idiosyncrasy to glycerine can be determined only by trial.

When administered internally in doses of one or two ounces, glycerine acts as a gentle but very uncertain laxative. It was proposed many years ago as a substitute for cod-liver oil in cachectic diseases, but has failed to come into use. It has also been highly commended in diabetes, but is of no service.

PETROLATUM.

Liquid petrolatum, or mineral oil, which is also known under a host of proprietary names, is recognized by the Pharmacopœia in two forms, the heavy and light. The latter has a specific gravity of 0.830 to 0.870, and the heavy from 0.875 to 0.905, and is a much more viscous fluid than the light. The light is intended for atomization, the heavy for internal use.

The composition of petrolatum, and consequently of liquid petrolatum, will vary according to the source of the original crude oil. There is a widespread but erroneous opinion that there is a consistent difference between Russian and American oils. All varieties of oils are found in this country. The best oils are those of the polynaphthene series.

Petrolatum acts mechanically on the skin like the fats, over which it has the advantage that it does not become rancid. The soft petrolatum is used as an emollient to the skin, and as a basis for ointments. The liquid petrolatum is used in the form of a spray as a soothing application to inflamed mucous membranes of the nose and throat. When taken internally these substances are incapable of absorption and, therefore, exert no influence on the system, but act locally upon the intestinal tract, allaying irritation and provoking soft fecal discharges, and the liquid petrolatum has a great vogue as a laxative.

COUNTER-IRRITANTS.

Almost from time immemorial physicians have believed that morbid processes in deep-seated or superficial organs could be modified by irritations artificially induced in distant parts. To the drugs used for producing these remedial irritations the name of revulsants, or counter-irritants, has been given, the process being called revulsion, or counter-irritation.

The question as to the manner in which a counter-irritant acts is essentially distinct from the question whether it does or does not act. However crude and uncertain our theories may be, clinical experience has demonstrated the value of counter-irritants in various internal conditions. It is proved beyond cavil that internal morbid processes may at times be relieved by creating external irritations. The old theory of the mode of action of the counter-irritants is that there is only a certain amount of blood in the body, and that if the blood be drawn to one part there must be less in another part. Surely, however, the amount of blood drawn to the skin by a mustard plaster is too small sensibly to affect the general mass in the body. It is more probable that the phenomena of counter-irritation are the result of reflex disturbances of the vasomotor nerves which influence the size of the blood-vessels, or of the trophic nerves which directly affect nutrition.

It is of great practical importance to know where the counter-irritant should be placed to affect most powerfully any given internal organ. We have no thoroughly scientific experimental knowledge as to this matter, but it has been clinically demonstrated that the general law for deep-seated parts is that the revulsant should be put directly over the part. When a superficial action is desired, other directions are needed. We are indebted to Anstie for pointing out what appears to be a law, or at least a good working rule for practice—namely, that when a superficial part supplied by the anterior branches of a spinal nerve is to be affected the counter-irritant should be placed over the posterior roots of the nerve. Not only can obstinate neuralgia often be relieved by this reflex action but also the inflammatory changes so often coincident with intercostal neuralgia.

The counter-irritants may be conveniently divided into two groups —those which are used simply to cause irritation and congestion without decided alterations of the dermal structure, the rubefacients, and those which produce severe structural changes. In the latter class belong the hot iron, the seton, and other destructive appliances, as well as epispastics, or vesicatories, commonly known as blisters.

While it is difficult to make any hard and fast rule which shall determine the conditions leading to a choice between the rubefacients and a blister, it may be said in a general way that the rubefacient is to be preferred where it is desired to produce a milder and more prolonged counter-irritation, especially for the relief of congestion, but when an intense effect for a limited area is desired the blister is to be chosen. In deep-seated inflammations, especially when there is struc-

tural change in the underlying organs, as in neuritis, the blisters are usually the more efficacious remedies, although when there is a considerable amount of tissue involved the rubefacient may even here be more useful.

Blisters are especially useful in inflammations of serous membranes, such as pleuritis and peritonitis; are very strongly recommended by some practitioners in parenchymatous inflammations, such as pneumonia. The amount of serum which is poured out from a blister is sometimes quite large, and vesicants have been even em-

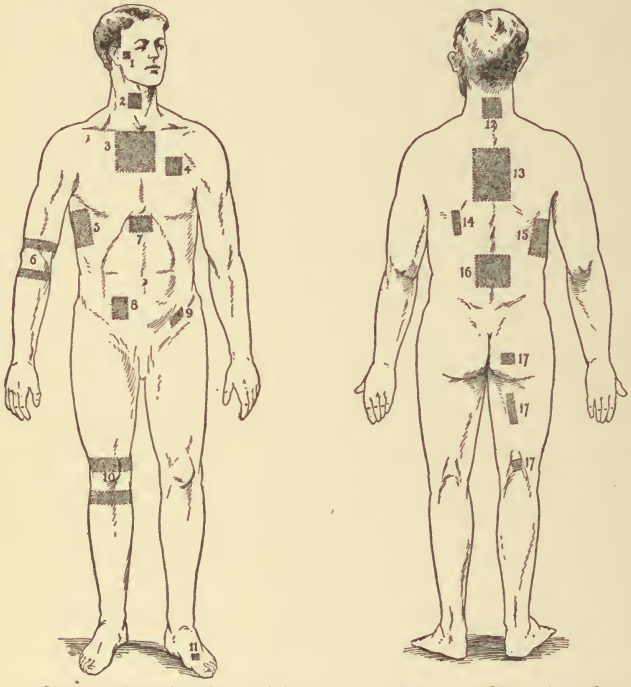


FIG. 28.—Showing the points for applying counter-irritants. 1, blister for inflammation of facial nerve; 2, blister for aphonia, mustard plaster for laryngitis; 3, mustard plaster for bronchitis; 4, blister or rubefacient in pericarditis; 5, blister or rubefacient in pleurisy or pneumonia; 6, rubefacient in rheumatic or other inflammation of elbow-joint; 7, blister for excessive vomiting, mustard plaster for gastralgia; 8, blister or rubefacient in appendicitis or colitis; 9, blister for ovaritis; 10, rubefacient in rheumatism of knee; 11, blister for gout; 12, blister in meningitis; 13, mustard plaster for bronchitis; 14, blister for intercostal neuralgia; 15, rubefacient in pneumonia; 16, rubefacient in lumbago, cupping in nephritis; 17, various points for blisters in sciatica.

ployed to relieve local dropsies, as, for example, serous effusion into the pleural sac or into the pericardium; they often do good, not only by affecting favorably the disease-process, but also by hastening the removal of the effusion. An irritation of the sensitive nerve in the normal animal produces an immediate vasomotor spasm, and in certain conditions of the body irritation of the mucous membrane or of the skin is of great service in stimulating respiration or circulation. Especially are they valuable when there is wide-spread loss of func-

tional activity in the vasomotor system, as in shock following injuries, in the first stage of pernicious malarial fever, and in other cases when the powers of the system are seemingly overwhelmed by some depressing agency.

Practically the only agent of this group which is used as a general stimulant is mustard, in the form of the so-called mustard bath, which is made by adding a tablespoonful of ground mustard for each gallon of water.

To the careful use of rubefacients as counter-irritants there are scarcely any contra-indications; but some caution is necessary in their application. A severe internal irritation may so successfully counter-irritate the external counter-irritation that the latter has for the time being no apparent effect, and yet really exerts a disorganizing influence. Thus, a mustard plaster, under the circumstances named, may at the time of its application produce no pain or redness, and yet twenty-four hours afterwards disorganizing inflammation may set in at the seat of the application. When there is severe internal irritation the counter-irritant should always be removed when it has been applied long enough to endanger violent local effects, even though it has exerted no sensible influence.

MUSTARD.

Materia Medica.—The United States Pharmacopœia recognizes two forms of mustard: white mustard (*sinapis alba*), the seeds of *Sinapis alba*, and as black mustard (*sinapis nigra*) the seeds of *Brassica nigra*. Both of these plants are European crucifers cultivated in the temperate regions of the world.

Black mustard seed contains a glucoside known as sinigrin or potassium myronate, and a ferment myrosin. In the presence of water the latter causes a decomposition of potassium myronate and a formation of an intensely irritant body, allyl-isosulphocyanate, more commonly known as the oil of mustard. It is a colorless, yellowish fluid with an intensely pungent odor and taste. A momentary contact with it suffices to redden and blister the skin, and mucous membranes are said to be rapidly destroyed by its vapors.

White mustard contains *sinalbin*, which in the presence of water and emulsin forms *acrinyl sulphocyanate*, an oily, non-volatile, very acrid substance, upon which the activity of white mustard depends.

Official Preparations:

Charta Sinapis [Mustard leaves].....External use.
Oleum Sinapis Volatile.....External use.

Therapeutics.—Mustard affords a most excellent material for the practice of mild revulsion. One advantage it possesses is the ease with which it can be controlled, all grades of action, from the mildest impression up to severe blistering, being at the will of the practitioner. It should be remembered, however, that the blister produced by it discharges but little, and is exceedingly sore and painful, as well as very slow and difficult of healing: so that, as an epispastic, mustard

is in every way inferior to cantharides, and should not be employed. The black mustard is much stronger than the white, and must usually be diluted at least one-half (by the addition of flour or of flaxseed meal). The white variety may sometimes be employed pure, but generally it also should be reduced in strength.

In many cases it is desirable to maintain for hours a mild, equable counter-irritant impression, and this may be done by adding from one to three teaspoonfuls of mustard, more or less, to a poultice of flaxseed. A mustard poultice (half-and-half black mustard, three parts to one of white mustard and flour) may generally be left on from twenty minutes to half an hour without danger of blistering. Weaker preparations may be used longer.

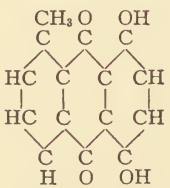
The so-called mustard leaves of the drug stores—*Charta sinapis*—are generally too violent in their effects for the best results, and the home-made mustard plaster is superior.

ABRIN.

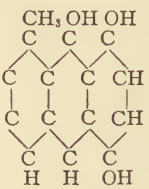
Abrin is a toxalbumin which occurs in the jequirity seeds obtained from the *Abrus precatorius*. These seeds are the size of a small bean, easily discernible by their bright red color, and by a black spot on one end. Abrin, like ricin, affects the system in a manner analogous to that of the bacterial toxins, and repeated injections produce an immunity which is due to the formation of an antitoxin. This antitoxin has also been put on the market under the name of Jequiritol Serum. Both the seeds and their active principle, abrin, are intense irritants capable of causing a local inflammation. Abrin is sometimes employed in ophthalmology for the purpose of causing a local inflammation of the eye in the treatment of pannus, especially when caused by trachoma. It is usually recommended in strengths of one to five-hundred thousand, and must be used with great caution, as an injudicious application has caused complete destruction to the eye.

CHRYSAROBIN.

Under the names of araroba and goa powder has long been employed, in Brazil, a substance which is found in the cavities of the trunk of a South American tree, the *Vouacaporia Araroba*. This powder is composed largely of the neutral principle chrysarobin, which is chemically closely allied to chrysophanic acid (see page 259).



Chrysophanic Acid.



Chrysarobin.

Chrysarobin is a yellow powder without odor or taste, but very irritant to the mucous membrane. It is practically insoluble in water, and only sparingly soluble in alcohol, but it is dissolved readily by solutions containing potassium hydroxide with the formation of an intense, brownish-red color. The Pharmacopœia recognizes, besides chrysarobin itself, a 10 per cent. ointment, *Unguentum chrysarobini.*

Therapeutic Uses.—Chrysarobin is used in medicine almost solely as an external application in skin diseases in which excessive scale formation is a feature, such as in psoriasis, or chronic eczema. Its value depends upon its affinity for oxygen, which restrains the proliferation of epithelial cells. It may be applied in the form of ointment of which a small quantity should be rubbed in vigorously once or twice a day. A great objection to this method of application, however, is the staining of the clothing as well as the skin, which is almost unavoidable. A more popular method of application is to paint the part with a 10 per cent. solution in collodion, which may be repeated every few days as the film becomes detached.

A great drawback to the use of chrysarobin is that it stains the linen an indelible mahogany color, as well as the skin. For this reason various derivatives of chrysarobin have been suggested as substitutes; among these may be mentioned *anthrarobin,* and two combinations with acetic acid known commercially as *eurobin* and *lenirobin.* These are employed in the same manner as chrysarobin.

CANTHARIDES.

Materia Medica.—This is the dried bodies of the *Cantharis vesicatoria,* a beetle, native in Southern Europe and commonly known as Spanish flies. They are from one-half to one inch in length and from one-sixth to one-fourth of an inch in breadth, have a large, heart-shaped head and brilliant, metallic-green wing-cases. Their odor during life is very strong and fetid, lost in drying; their taste is urinous, very burning, and acrid. When ground, Spanish flies afford a grayish-brown powder, full of minute greenish spangles, the remains of the feet, head, and wing-cases. The active principle of cantharides is *cantharidin,* which occurs in white crystalline scales, is inodorous, tasteless, insoluble in water, nearly so in cold alcohol; soluble in ether, benzole, the oils, and also very freely so in chloroform. Notwithstanding the insolubility of pure cantharidin, Spanish flies yield their virtues to alcohol and to water.

Official Preparations:

Ceratum Cantharidis	External use.
Collodium Cantharidatum	External use.
Tinctura Cantharidis (10 per cent.)	1 to 2 minims (0.06–0.12 mil).
Emplastrum Cantharidis	External use.

Physiological Action.—Cantharides is very irritating, and, when applied to the skin, causes at first redness, with burning, then free

vesication and severe pain, and, if the contact be longer maintained, deep inflammation and sloughing. Upon the mucous membranes it produces a no less intense effect. The cantharidin is rapidly absorbed. and is eliminated unchanged by the kidneys.

During their passage through the kidney, if the quantity is large, they may cause intense irritation of these organs, giving rise to an acute nephritis, and also of the bladder and urethra, causing strangury.

Therapeutics.—Cantharides was at one time employed internally as a stimulant to the genito-urinary organs in chronic inflammatory conditions and in amenorrhœa. It is also employed popularly in the treatment of sexual impotence. Any beneficial effect in this condition is due solely to its local irritant influence upon the mucous membrane of the genitalia.

For blistering, the plaster is to be preferred. This is made by spreading the cerate on rosin plaster in such a way as to leave a margin to adhere to the skin and hold the plaster in its place. In order for a blister to "draw" thoroughly, it usually has to be left on some eight hours; but in most cases the same result can be achieved with less suffering by allowing the blister to remain only five or six hours, or until decided redness and slight vesication have been induced, and then applying a flaxseed poultice. In certain localities vesication requires a much longer application than that just spoken of; thus, upon the shaved scalp a blister will rarely act efficiently in less than twelve hours, and often not in that time.

Cantharidal collodion (*Collodium cantharidatum*), although far less certain in its effects than the plaster, may be used when there is any special danger to be feared from the absorption of the active principle; the use of the poultice after a brief application of the blister as described above should always be practised.

The *contra-indications* to the use of blisters are high arterial and febrile excitement and a decided want of vital power. In the former case, the irritating influence which they exert upon the general system may increase the constitutional disturbance to such an extent as to do more injury than any local benefit derived from them can do good. When the vitality is very low, blisters may give rise to sloughing ulcers, which, refusing to heal, may waste very seriously the already exhausted system. Great care must be exercised in their employment in the very young or the very aged. Very rarely indeed is a blister called for in the case of a young infant, and if it be employed at all, it should be allowed to remain in contact with the skin only long enough to produce slight pain or redness, and the complete vesication should be obtained by the after-use of a poultice.

Toxicology.—Toxic dose of cantharides produces in a few minutes a burning pain in the pharynx, œsophagus, and a sense of stricture in the throat, soon followed by epigastric pain and vomiting, and later, in the majority of cases, by purging. The matters vomited are at first

mucous, showing, if the drug has been taken in a powder little greenish specks through them; then bilious and finally bloody. The stools are mucous, then fibrinous and bloody, often very scanty but excessively numerous and their passage accompanied by great tenesmus. In most cases severe salivation is developed early in the poisoning, frequently accompanied by great swelling of the salivary glands, burning pain in the genito-urinary tract with complete strangury as a characteristic symptom of the poisoning. Aching pain in the back and frequent micturition indicate a commencing urogenital irritation. These symptoms increase in intensity until there is a constant, irresistible desire to urinate, with violent tenesmus of the bladder, and yet an inability to pass more than a few drops of urine, which is albuminous, and not rarely bloody. In some cases there is a violent erotic excitement, an unquenchable lust, accompanied in man by numerous seminal emissions; violent priapism, swelling and heat of the organs, and even severe inflammation of the parts may indicate the intensity of the local action of the poison; sometimes gangrene ultimately occurs. Consciousness and general power are often long preserved when the local symptoms and agony are intense, but, if the dose has been large enough, sooner or later collapse comes on with the usual accompaniments, and the prostration deepens into complete powerlessness, stupor, coma, and, finally, death. After death from cantharides there are found intense hyperæmia of the kidneys and mucous membrane of the bladder, and, if the poison has been taken by the mouth, also of the alimentary tract, with patches of exudation and loss of epithelium. The changes in the kidney involve chiefly the glomeruli.

There is no known antidote to cantharides, and the treatment of the poisoning must be conducted on general principles. If the remedy has been taken by the stomach, this should be washed out rapidly with large draughts of warm water or emptied, if the stomach-pump be not at hand, by means of an emetic; large quantities of mucilaginous or albuminous drinks should be administered for their demulcent effects, but all oily substances should be avoided as favoring the solution, and hence the absorption, of the poison. Opium should be freely exhibited to allay pain and relieve the strangury.

ESCHAROTICS.

Escharotics or caustics are substances which are used for the purpose of destroying tissue. They act in various manners. Some destroy the viability of the part, which subsequently sloughs off as any other dead tissue would do; others act by a solvent effect, liquefying the tissues. The first group, of which arsenic is the type, act much more powerfully against unhealthy tissue and morbid growths than they do against normal cells. The second class, as represented by the alkaline hydroxides, act equally powerfully against healthy as against diseased tissue.

The caustics are used primarily for the purpose of destroying tissue. In poisoned bites, as of rabid animals, or in badly infected wounds they prevent systemic intoxication, partially by virtue of their germicidal influence, but also because the destruction of underlying tissue delays absorption. They are also employed to destroy superficial growths, whether benign—as warts or nævi—or malignant—as epithelioma or lupus. There is at present a disagreement as to whether the knife or the escharotic is more likely to prove permanently curative in superficial cancers, but there is no room for doubt that in proper cases, when skilfully used, the caustics are valuable remedies.

A number of substances which are employed as caustics are considered elsewhere in this work. These include the caustic alkalies, potassium, sodium hydroxide, nitric acid, the caustic metallic salts, such as zinc chloride, mercuric chloride, silver nitrate, etc. There are some agents, however, which are used for no other purpose than as caustics, which are briefly considered in this place.

Pyrogallol.—This substance which is also known as pyrogallic acid is a trihydroxybenzene. It is manufactured by decomposing gallic acid. It occurs as colorless crystals readily soluble in either water or alcohol. It has a strong affinity toward oxygen, especially in alkaline solution. It is not used internally.

Physiological Action.—Pyrogallol is a powerful irritant and in concentrated solution caustic. It is much less active than phenol as a germicide.

When taken internally pyrogallol is an active poison; the symptoms which it causes being due in part to its local irritant effect, partly to its action on the central nervous system and partly to its effect upon the blood. On the central nervous system it appears to act much like phenol.

It has an intensely destructive action on the red blood-corpuscles, dissolving out their hæmoglobin. The hæmoglobin after it is dissolved into the blood-serum becomes converted into methæmoglobin, causing the blood to take on a characteristic chocolate color. If death does not occur too soon the destructive action on the blood is manifested by icterus and by methæmoglobinuria.

The irritant action in pyrogallol poison is exerted not only upon the alimentary tract—as is shown by the vomiting and purging—but also upon the kidneys, giving rise to an acute nephritis with or without hæmaturia.

Therapeutics.—Pyrogallol is used in medicine solely as a local agent in various skin diseases, especially psoriasis. Its value in these conditions depends upon its strongly reducing effect and perhaps in part also upon its antibacterial properties. It produces a brownish discoloration on the skin and also a permanent stain on the clothing, with which it may come in contact. It is to be remembered that pyrogallol can be absorbed through the skin and serious poison has resulted

from its external application. It may be applied to the skin in the form of an ointment containing from 5 to 10 per cent.

Because of the toxic powers of pyrogallol, various allies have been brought forward as substitutes; among these may be mentioned lenigallol (pyrogallol triacetate), and eugallol (pyrogallol monoacetate). In gallacetophenone or alizarin yellow the acetyl radical replaces one of the hydrogen atoms of the benzene instead of the hydroxyl. Lenigallol and gallacetophenone are usually applied in the same manner as pyrogallol; eugallol, which is marketed in the form of a 66 per cent. solution, is, however, generally applied full strength.

Chromium Trioxide, commonly known as *chromic acid*, occurs in anhydrous acicular crystals, of a deep purplish-red color, and an acid, metallic, corrosive taste. They are very deliquescent, melting down, when exposed to the air, into an orange-red solution. Chromium trioxide is a very active oxidizer, and will dissolve almost any form of tissue. It is used to destroy condylomata and other dermal growths, and is best applied by means of a glass rod, the liquid formed by the spontaneous deliquescence of the crystals being used. In the German army, painting the soles of the feet and the skin between the toes with a five per cent. solution of chromic acid is said to have had a very great influence in increasing the marching powers of the troops, by arresting excessive sweating, and hardening the skin. Chromic acid is a violent corrosive poison, a single drop of the saturated solution having caused very severe symptoms. The nature of the poison may often be recognized by the reddish-brown, or more rarely greenish, discoloration of the skin of the lips and of the mucous membrane of the mouth and gullet, but this discoloration may be absent. In a number of cases death has resulted from the too free external use of the acid.

Lactic acid is formed in various fermentations. The official lactic acid of the United States Pharmacopœia is a liquid containing not less than 75 per cent. of lactic acid.

Lactic acid was at one time attributed with narcotic properties, but to-day it is used solely as a mild caustic, especially in tuberculous ulcers of the larynx or skin and in various infections of the mucous membranes. It may be used in from five to ten per cent. solution.

Trichloracetic acid (CCl_3COOH) is obtained by oxidizing chloral hydrate with nitric acid. It occurs in the form of deliquescent crystals which are freely soluble in water and alcohol. It has been used to a considerable extent for the destruction of papilloma and other growths; a single crystal placed on a growth produces immediately a white, dry, adherent mass, which falls off in a few days. It is also used in very dilute solutions—one part in one or two thousand of water—in chronic catarrhs of the nose and pharynx. As a caustic it has the advantage over many other agents in producing much less pain. A solution made by adding one part of water to nine parts of the acid may be employed; it is advisable to protect the skin in the neighborhood of the application by previously painting with collodion.

PROTECTIVES.

BISMUTH.

Materia Medica.—Metallic bismuth is not used in medicine, but a large number of its insoluble salts have been employed, and the Pharmacopœia recognizes four of them. The oldest and probably most widely used is the so-called subnitrate or oxynitrate ($BiONO_3$). This is a heavy, odorless, tasteless white powder completely insoluble in all menstruua except strong mineral acids. As it appears commercially it generally contains a small amount of free nitric acid. Bismuth subcarbonate ($Bi_2O_2CO_3$) is a pale yellowish-white, insoluble, odorless, and tasteless powder which gives up its carbon dioxide in the presence of acids and is converted into the anhydrous trioxide. The subgallate is a bright yellow powder of somewhat variable composition which is insoluble in water but readily soluble in solutions of the alkaline hydroxides. Bismuth subsalicylate is a nearly white, amorphous, or crystalline powder, odorless and tasteless.

Besides these insoluble salts of bismuth, the Pharmacopœia recognizes a soluble salt of bismuth and ammonium citrate which occurs in small, shining, translucent scales with a metallic, astringent taste. Its action upon the system is entirely different from the other salts of bismuth, and there is no excuse for its inclusion in our therapeutic armamentarium.

Official Preparations:

Bismuthi Betanaphtholas	5 to 15 grains (0.3–1 Gm.).
Bismuthi et Ammonii Citras	2 to 3 grains (0.1–0.2 Gm.).
Bismuthi Subcarbonas	5 to 60 grains (0.3–4.0 Gm.).
Bismuthi Subgallas	5 to 30 grains (0.3–2.0 Gm.).
Bismuthi Subnitras	5 to 30 grains (0.3–2.0 Gm.).
Bismuthi Subsalicylas	5 to 30 grains (0.3–2.0 Gm.).

Physiological Action.—The official salts of bismuth are so extremely insoluble that not sufficient of them can be absorbed to exercise any bismuth effect upon the bodily functions.*

When introduced into the circulation, however, bismuth has a marked effect upon the system. In large doses it causes a primary stimulation of the nerve-centers, followed by a secondary depression, with marked lowering of the blood-pressure and symptoms of irritation of the excretory organs.

The therapeutic value of bismuth depends almost solely upon its physical properties, although it is possible that it may exercise a mild

* A number of cases of poisoning have resulted from the administration of large quantities of bismuth subnitrate for the purpose of X-ray examination of the alimentary tract. These poisonings have, however, been shown to be due to the formation of a nitrite, and do not occur after the use of other salts of bismuth.

astringent influence. The preparations of bismuth, being heavy and insoluble, tend to cling to any surface with which they are brought in contact; after the administration of a bismuth salt by the mouth they gradually spread themselves over the gastro-intestinal mucous membrane and undergo a slow conversion into the black oxide of bismuth. This coating of the mucous membrane protects it against the action of any irritant substance precisely analogously to the way in which white lead protects buildings from the effects of the weather. The salts of bismuth, as sparingly soluble as they are, have been shown to be possessed of distinct antiseptic powers. Their therapeutic virtues rest on a combination of these three properties—feeble astringent influence, antiseptic effect, and a mechanical protective effect.

Therapeutics.—The insoluble salts of bismuth are used chiefly in the treatment of inflammations of mucous membranes. They are useful in all acute catarrhs in which they can be brought in local contact with the inflamed membrane.

Thus the suspension of bismuth subnitrate in mucilage makes a useful application in the treatment of acute coryza. The most frequent employment, however, of the bismuth salts is in inflammatory conditions of the alimentary tract. In acute gastritis and the various forms of acute enteritis they are among the most generally useful remedies that we possess. In inflammations of the stomach they will often relieve vomiting or pain, but they do this solely by protecting the mucous membrane from the irritant contents of the stomach and not by any specific action upon the nervous mechanism. In gastric ulcer bismuth subcarbonate in large doses affords perhaps the most useful medicinal treatment known. In inflammatory conditions of the intestines the bismuth salts are most frequently of service in the acuter types of enteritis. Their astringent action is very feeble and they are of little service in controlling free serous purging.

Bismuth subnitrate has also been used to a considerable extent in surgery. As a dusting powder for wounds it is desiccant, protective, and mildly antiseptic, and may be used in the same class of cases for which iodoform is applicable. A paste consisting of one part of bismuth subnitrate with two of petrolatum has been injected into fistulæ due to bone tuberculosis, with good effects, in a large number of cases.

Either of the surgical uses of bismuth is liable to be followed by severe or even fatal intoxication. One of the earliest signs of bismuth poisoning is a line on the gums which varies in color from a greenish-blue to black. The other characteristic symptoms are acute stomatitis, sometimes gangrenous, with a peculiar blackish discoloration of the mucous membranes, usually beginning upon the borders of the teeth but spreading over the whole mouth; gastro-intestinal catarrh with pain, vomiting and diarrhœa; and, in severe cases, acute nephritis with albuminous urine and tube casts. The treatment, aside from removing the bismuth, is purely symptomatic.

Administration.—In order to get the best results from the use of bismuth salts it is necessary to vary the dose and method of administration. In ordinary cases of gastritis from five to ten grains may be given at a dose, preferably an hour or two before meals, so that the remedy may have a chance to spread itself over the gastric mucosa before it is carried out into the intestinal tract by the active peristalsis; a number of authorities have claimed to have obtained extraordinary results by the use of large doses, two to four drachms, of bismuth subcarbonate. In enteritis the dose should be not less than twenty or thirty grains and administered, preferably, an hour or two after meals, so that it will be carried on into the intestinal tract by the peristaltic movements of the stomach.

BISMUTH.

Balzer.....C.R.S.B., 1889, 9s. i, 537.
Dalché and Villejean.....B.G.T., 1888, cxv, 404, 448.
David and Kaufmann.....J.A.M.A., 1909, lii.
Schmidt.....W.K.W., 1911.
Steinfeld.....A.E.P.P., 1885, xx, 41.

CERIUM OXALATE.

Under the name of cerium oxalate, the United States Pharmacopœia recognizes a mixture of the oxalates of cerium, didymium, præsodymium, lanthanium, and other rare earths. It is a white powder insoluble in water or alcohol, but soluble in hot dilute hydrochloride or sulphuric acid. There is a superstition among clinicians that this remedy possesses peculiar virtues in relieving emesis, but its value is probably simply that of a chemical protector and in no wise superior to bismuth.

CHAPTER IX.

DRUGS OF MINOR IMPORTANCE.

In this chapter are included a number of remedies which are, largely out of a respect for the practices of the ancients, recognized by the United States Pharmacopœia. While for a few of them there is much clinical support, we know little or nothing definite of their effects; indeed, most of them do not apparently modify in any sensible degree the normal functions of the body.

CALMATIVES.

In certain conditions of the nervous system, conditions associated with weakness rather than simple depression, the nerve-centers appear to be more susceptible than normal to external impressions, as well as to those impulses which originate in the cerebral centers themselves and are connected with the emotions. As a result of this state arise symptoms ranging in their intensity from the simple state of unrest known as nervousness to the wildest convulsion of hysteria. There are a number of drugs which have been used with apparent benefit in this class of conditions. It is noteworthy that none of these substances have been shown to be endowed with any great physiological power, but that each possesses a strong odor and flavor. This weakness of physiological properties and strength of physical properties has led to the belief that their virtues are chiefly psychical; that the powerful odor leads to a belief that they are powerful remedies, and that the cerebral control is stimulated by suggestion, for the superstition that the worse the taste of a remedy the more potent it is still survives to a surprising extent even among the educated. The thoughtful physician clearly apprehends that the beneficial effects of drugs are not always due merely to a direct action upon diseased organs, but that frequently a part, if not the greater part, of the good effects which they produce are the result of a patient's expectations of relief. Practically all of the organs of the body can be influenced by psychical factors; it has been experimentally proven that it is possible to cause dilatation of the vessels of an extremity merely by concentrating the mind upon that part, and the increased secretion of saliva when thinking of appetizing foodstuffs, the diuresis which is the result of anxiety, and the increased action of the heart under emotional stress are familiar examples of the influence of the mind over the body; and it is not impossible that agents such as valerian and serpentaria, whose flavor is striking and peculiar, depend for their remedial virtues on their physical rather than their physiological properties.

Many clinicians, however, believe that these remedies do exercise some direct influence upon the cerebrum. Because the changes in

cerebral activity—assuming that the cerebrum is the site of the emotions—are, except in their most extreme manifestations, almost purely subjective in character, it is manifestly impossible to carry out satisfactory experimental investigations into the effects of drugs upon intellectual processes, so that our lack of knowledge concerning the effects of these substances upon cerebration is not final proof that they are inert in this regard. All that we can say of them is that we know of no direct action upon the brain or generally on any other function.

It is to be pointed out that their effects are very different from the cerebral depressants, such as the narcotics of the methane homologues, and that the latter are of relatively little value in those states in which the present class are generally employed.

The drugs which are used as calmatives in hysterical and semi-hysterical states are: asafœtida, cimicifuga, cypripedium, hops, musk, sumbul, and valerian. Camphor, which is also used as a quieting agent, is considered elsewhere (p. 196).

VALERIAN.

Materia Medica.—The rhizome and roots of the *Valerian officinalis*. This European plant is an herbaceous perennial, growing to a height of from two to four feet, with pinnately compound leaves, and small, pinkish flowers in compound cymes.

The official portion consists of a short, yellowish rhizome with numerous fibrous roots. It has a strong, disagreeable odor and a bitter, camphoraceous taste. Valerian depends for its activity upon a volatile oil and the valeric acid esters which it contains.

In the belief that the activity of valerian resides in the valeric acid various esters and salts of this acid have been employed. The official ammonium valerate occurs as colorless, quadrangular plates, deliquescent, with the characteristic odor and a sharp, sweetish taste, very soluble in both water and alcohol. Besides this salt, the zinc valerate and various organic derivatives of valeryl have been largely employed in medicine.

Fresh valerian root has a not unpleasant aromatic odor, but when kept it develops a strong, disagreeable one, due to the oxidation of the esters, composing its volatile oil, to valeric acid. As any virtues the drug possesses probably reside in the volatile oil, it is manifest that the dried root is inferior to the fresh.

Official Preparations:

Tinctura Valerianæ (20 per cent.).....1 to 3 fluidrachms (4–10 mils).
Tinctura Valerianæ Ammoniata (20 per cent.) 1 to 3 fluidrachms (4–10 mils).
Ammonii Valeras .....10 grains (0.6 Gm.).

Therapeutic Uses.—According to Chevalier (*Nouv. Rem.*, 1912, xxix, 169), valerian is a sedative to the entire central nervous system, including the medulla and cord, and has a mild stimulating effect on the

circulation. It is probable that the valeryl derivatives act like the other aliphatic derivatives. Valerian is one of the most popularly esteemed remedies of this class for the treatment of hysteria, nervousness, neuralgia, and similar functional disorders. Whether its effects are due entirely to the psychic effect of its potent flavor or not is doubtful, but the fact that valeric acid and its esters are widely employed in forms in which the taste is entirely disguised indicates that it may possess some direct sedative power.

HOPS.

Materia Medica.—Under the term *Humulus* the Pharmacopœia recognizes the strobiles (fruit) of the hop vine, a perennial herbaceous twiner which is largely cultivated both in this country and Europe. The strobiles are soft, greenish cones, one or two inches in length, composed of thin, leaf-like, imbricated scales, having a bitter taste and a heavy narcotic odor. At the bases of the scales is a yellowish powder, lupulin, which contains, according to Payen, two per cent. of volatile oil, 10 to 30 per cent. of bitter principle, and fifty to fifty-five per cent. of resin. The volatile oil of lupulin contains valerol, which, on keeping, is gradually oxidized to valeric acid.

Hops is a bitter tonic and a very feeble narcotic. It has been used in the milder types of sleeplessness and to quiet general nervousness, and appears at times to exercise a favorable influence. It is also of service as a bitter tonic in cases of digestive failure. It may be given in doses of from one-half to one drachm (2–4 Gm.).

LACTUCARIUM.

Materia Medica.—Under the term of lactucarium the United States Pharmacopœia recognizes the "concrete milk juice of the *Lactuca virosa,*" or strong-scented lettuce, a plant closely allied to the common lettuce of our tables; the juice of the latter is also supposed to possess the same therapeutic virtues. The juice is obtained by cutting the heads off each stalk and scraping the juice which exudes into vessels, repeating the operation several times a day until the plants are exhausted. This, when dried, comes into the market in small, irregular lumps of a reddish-brown color, of a bitter taste, and an odor like that of opium. Probably because of the similarity in its odor to this powerful narcotic, lettuce juice has been supposed to be possessed of somnifacient properties. Such hypnotic influence as it exercises, however, must be purely by the process of suggestion. The superstition of its sedative power probably arose from the use of a syrup of opium and lactucarium which was formerly very popular.

Official Preparations:

Tinctura Lactucarii (50 per cent.).....1 to 2 fluidrachms (4–8 mils).
Syrupus Lactucarii (15 per cent.).....½ to 1 fluidounce (15–30 mils).

CIMICIFUGA.

Materia Medica.—The *Cimicifuga racemosa,* or black snake-root is an indigenous plant, growing abundantly in shady woods, attaining a height of six or seven feet, and readily distinguished by its very large, multi-compound leaves and its long-branched spikes of whitish, polyandrous flowers, naked when open. The official portions consist of a knotted head, with numerous fine, brittle rootlets: the odor is faint, and the taste bitterish, somewhat astringent, and acrid. The nature of its active principle has not been determined. The tendency of the drugs to deteriorate on keeping indicates the presence of a volatile principle.

Official Preparations:

Extractum Cimicifugæ .....5 to 15 grains (0.3–1.0 Gm.).
Fluidextractum Cimicifugæ .....20 to 60 minims (1.2–4.0 mils).

Physiological Action.—Hutchinson found that large doses acted on frogs as a depressant of the sensory side of the spinal cord, producing complete anæsthesia with loss of reflex activity at a time when voluntary movement was still preserved. Upon the circulation cimicifuga acts as a depressant, producing, in the mammal, fall of the arterial pressure and slowing of the pulse, and causing finally diastolic arrest of the heart. As the slowing of the pulse is not prevented by previous section of the vagi, and as the isolated frog's heart becomes slow and in a little while paralyzed after direct contact with the cimicifuga, it is evident that the drug acts as a direct depressant to the heart muscle; but the fall of blood-pressure appears to be due to depressant influence on both heart and blood-vessels.

In man, although there have been no serious cases of poisoning, large doses have given rise to dizziness, headache, and reduction in the pulse-rate, with, in some instances, nausea and vomiting.

Therapeutics.—Cimicifuga was originally proposed by Young, in 1831, as a remedy in chorea, and in the simple chorea of childhood its value is unquestionable. It must be given until it produces physiological effects, and in most cases the consentaneous exhibition of iron and laxatives materially aids it. Cimicifuga has also been used with more or less favorable results in urticaria, chronic rheumatism, and various pelvic disorders, as ovarian neuralgia or dysmenorrhœa.

MUSK.

A highly odorous, unctuous substance, obtained from the glands situated just in front of the preputial orifice of the *Moschus moschiferus,* or musk-deer of Thibet. As it occurs in commerce, musk is very greatly adulterated.

Because of the difficulty of obtaining it pure, as well as its expensiveness, musk is at present very little used, but has been extraordinarily lauded by some of the older writers in hiccoughs, and in the exhaustion of low fevers, as typhoid and adynamic pneumonia.

ASAFŒTIDA.

An exudation obtained by incising the living root of the *Ferula fœtida,* an umbelliferous plant of Afghanistan. It occurs mostly in irregular, opaque masses of a dull yellowish or pinkish brown, white when freshly broken, with a bitter, acrid taste and a powerful, persistent odor resembling that of garlic. Although 90 per cent. of asafœtida is made up of gum and resin, its virtues are probably due to the volatile oil, of which it contains from three to nine per cent.

Official Preparations:

Pilulæ Asafœtidæ (each 3 grains).....2 to 4 pills.
Tinctura Asafœtidæ (20 per cent.).....½ to 1 fluidrachm (2–4 mils).
Emulsum Asafœtidæ (Milk of Asafœtida)
(4 per cent.).....4 to 8 fluidrachms (15–30 mils).

Therapeutics.—Asafœtida is one of the most efficient carminatives we possess, and is constantly used, especially in children, in the form of an enema for the relief of tympanites and flatulent colic. It is also valuable as an addition to laxative pills for the purpose of stimulating peristalsis. It was formerly largely employed in various hysterical spasmodic states and also as a stimulant expectorant, but has been largely adandoned for less unpleasant remedies.

SUMBUL.

Under this name the United States Pharmacopœia recognizes the root of the *Ferula Sumbul* which comes from Central and Western Asia. It has a bitter taste and a strong, musk-like odor. It contains a volatile oil, a balsamic resin, and angelic acid.

Official Preparations:

Extractum Sumbul ..... 5 to 10 grains.
Fluidextractum Sumbul .....½ to 1 fluidrachm.

Therapeutic Uses.—Sumbul is widely employed as a nerve sedative in those states in which valerian is useful, but is especially esteemed for the relief of various symptoms referred to the pelvic organs in neurotic women.

VIBURNUM.

The Pharmacopœia recognizes under this title the barks of the *Viburnum prunifolium* and *V. lentago,* large shrubs which are common in various parts of the United States. Viburnum contains a resinous principle known as viburnin, and also some valeric acid.

These barks have been used in various uterine disorders, but there is no convincing evidence that their effects differ from those of any other disagreeably-tasting substance. It is true that Sheeran has found that very large doses have a depressant action on the motor side of the spinal cord, but he himself took six drachms of the fluidextract with no perceptible effect. The ordinary dose recommended is from thirty to sixty minims of the fluidextract of either species.

OLEORESIN OF PARSLEY.

The fruit of the ordinary garden parsley (*Petroselinum sativum*) yields an oleoresin which contains three closely allied principles, namely, apiol, apiolin, and myristicin, the latter identical with the toxic principle of oil of nutmeg. The term "apiol" has been applied to a host of different substances, and the term "liquid apiol" is frequently applied to the complete oleoresin. This occurs as a yellowish liquid with a characteristic odor and an acrid, pungent taste. It is recognized by the Pharmacopœia under the name of *Oleoresina Petroselini.* The dose of it is from 5 to 10 minims (0.3 to 0.6 mil).

The physiological action of the oleoresin of parsley has not been sufficiently investigated, but full doses produce paralysis, fall of blood-pressure, and some slowing of the pulse. According to Rimini and Delitala, the paralysis is preceded by violent convulsions and followed by fatty degeneration of the liver and kidney, similar to that caused by myristicin (see page 248).

The oleoresin of parsley has been supposed to exercise some specific action upon the female generative organs, and is a very popular remedy in amenorrhœa and dysmenorrhœa. This is, however, no sufficient evidence that it possesses any virtues beyond that of other volatile oils.

ALTERATIVES.

Another group of remedies which have come down to modern times with the sanction of tradition, but of whose value there is even less ground for belief, are those which have been attributed with some mysterious power of correcting morbid function, although they have little effect on healthy organs. These have been employed especially in chronic complaints in which it is difficult to determine whether the changes in the patient's condition have been because of or in spite of the treatment. It is worthy of note that these drugs are usually employed in conjunction with remedies whose efficiency is well known; thus the reputation of stillingia and sarsaparilla in syphilis is probably due to the fact that they are nearly always used with potassium iodide.

Taraxacum.—This is the dried root of the *Taraxacum officinalis,* the common weed known as dandelion. It has been attributed with diuretic and cholagogic powers, but is a useless herb, although still official.

Xanthoxylum.—The dried bark of the *Xanthoxylum americanum,* or prickly ash, has been supposed to possess valuable alterative properties, and consequently employed in the treatment of chronic rheumatism and syphilis. It is locally irritant and when chewed has been used as a counter-irritant in the treatment of toothache. It has also been employed externally as a rubifacient. The dose of the fluidextract is from fifteen to thirty minims.

Stillingia.—The root of the *Stillingia sylvatica,* popularly called Queen's delight, is a native plant. It was at one time supposed to possess alterative properties and was used in syphilis. It has, however, probably no therapeutic virtues. It is still retained in the Pharmacopœia because of an undue regard for ancient tradition.

Serpentaria.—Serpentaria is the dried rhizome and root of the *Aristolochia serpentaria,* or Virginia snake-root. It appears to contain a bitter principle, perhaps alkaloidal in nature. When taken in large dose it irritates the intestinal tract, causing nausea and griping pains. It was at one time supposed to possess antimalarial properties, and is still an ingredient in the compound tincture of cinchona. Its only possible therapeutic virtue is as a stimulant to the gastric mucosa.

Aspidosperma.—The bark of the South American tree *Aspidosperma Quebracho-blanco* contains six alkaloids: aspidospermine, aspidospermatine, aspidosamine, quebrachine, hypoquebrachine, and quebrachamine. Of these the most important are quebrachine and aspidospermine. The fluidextract is official; dose 30 to 60 minims (2–4 mils).

Physiological Action.—The various alkaloids of aspidosperma seem to have very similar actions, their most marked action being upon the respiration. They cause a great increase both in the depth and the rapidity of the breathing; in my own experiments the volume of air moved per minute was increased sometimes as much as four hundred per cent., although after the previous administration of powerful respiratory depressants the increase was usually much less marked and sometimes entirely lacking. The violent respirations which are characteristically produced by this drug were believed by Penzoldt to be due to an effect upon the blood which prevented the red corpuscles from giving up their oxygen. While it is true as originally observed by this author that in many cases the blood in the veins is of the arterial hue, it is probable that this is the result rather than the cause of the rapid breathing. When given in full dose the drug also produces a marked fall of the blood-pressure. This action is apparently caused chiefly by aspidosamine, although the other alkaloids act in a lesser degree as depressants to the heart.

Aspidosperma has been used chiefly as a remedy in various cases of dyspnœa, especially in asthma. According to Cohen, it is of little service during the asthmatic paroxysm, but has a marked action in preventing a recurrence of the attacks, although not truly a curative.

The fluidextract of aspidosperma may be administered in doses of from ½ to 1 fluidrachm (2–4 mils) every two or three hours, but is likely to produce nausea. Under the name of amorphous aspidospermine is sold a mixture of the several alkaloids of the bark; the dose of this preparation is about one grain. The pure crystalline aspidospermine may be given in doses of from $^1/_{40}$ to $^1/_{20}$ of a grain.

ASPIDOSPERMA.

Cohen .....Penna. Med. J., Dec., 1904.
Cow .....J.P.Ex.T., 1914, v, 341.
Wood .....U.P.M.B., Sept., 1903; March, 1910, xxiii.

APIOL.

Chevalier .....B.G.T., 1909, clviii, 101; 1912, clxiii, 467.
Lutz .....Bull. Sci. Pharm., 1909, xvi; 1910, xvii, 1
Rimini and Delitala.....Arch. Farm. e Terap., 1908, xiv, 293.

LOCAL IRRITANTS.

Staphisagria.—The *Delphinium staphisagria,* or stavesacre, is a large herb with purplish, showy flowers native to Southern Europe. The seeds, which are the official portion, are broad, irregularly four sides, generally curved on the broadest side, and about one-quartr of an inch long. They contain a characteristic alkaloid delphinine which appears to resemble aconitine in its physiological action.

Stavesacre is used only as an external remedy against lice and the itch mite, for which purpose it is very efficient. It may be employed either in the form of an ointment containing about 25 per cent., or the fluidextract may be diluted with two or three parts of alcohol. It is capable of causing serious poisoning if taken internally.

Mezereum.—The bark of the *Daphne mezereum*, an European shrub. It contains, besides a bitter glucoside, daphnine, which is probably medicinally inert, and an acrid resin, mezerein.

Mezereum, when fresh, is sufficiently irritating that when applied to the skin it is capable of causing vesication, and has been used as an epispastic for centuries. A piece of the bark moistened with vinegar and applied to the skin will usually blister within twenty-four to forty-eight hours. Although rarely employed in this country for the purpose of blistering, an ointment of mezereum is sometimes employed after cantharides blister for the purpose of maintaining a counter-irritant action where a powerful prolonged influence is desired. It is also employed as a stimulant application to unhealthy ulcers. Mezereum was at one time supposed to possess alterative properties and used in the treatment of syphilis and scrofula. This old superstition has led to its being included in the compound syrup of sarsaparilla.

Arnica.—Arnica is the flowering portions of the *Arnica montana*, a perennial composite native to Northern Europe and Asia. Both tubular and ligulate flowers, the latter being sixteen in number and three-toothed at the end, are bright yellow in color. The ray flowers are about an inch long. Arnica contains a glucoside which has been called arnicin. Various alkaloidal bodies have also been described, but their presence is doubtful.

Arnica, when locally applied, if in concentrated solution, is decidedly irritant, and, indeed, upon delicate skins may give rise to an

acute eczematous inflammation with vesiculation. The general effect upon the system has not been sufficiently studied. It appears to have a distinct influence upon the circulation, slowing the pulse and, according to some, also increasing its size.

Arnica has been employed by various irregular sects, but does not appear to possess any virtue, as an internal remedy. It is very widely employed as a household counter-irritant in sprains and bruises.

Pyrethrum.—This remedy, which is commonly known as pellitory, is the root of the *Anacyclus pyrethrum,* a perennial plant found around the Mediterranean coast. It contains an alkaloid pyrethrine, which has an intensely burning taste, as well as an acrid resin. Because of its irritant properties when chewed pellitory excites the secretion of the salivary glands, and is, therefore, spoken of as a sialogogue. It is used as a stimulant and irritant in toothache and relaxed conditions of the mouth. It is doubtful whether pyrethrum possesses any therapeutic virtues which are not common to all irritant substances.

Eriodictyon.—The leaves of the *Eriodictyon californicum,* an evergreen shrub found in Southern California and popularly known as yerba santa, are official. These leaves contain an acrid resin as well as a volatile oil. Eriodictyon has been used in the past as a stimulating expectorant in chronic bronchitis and asthma, but it is retained to-day chiefly for the remarkable property it possesses of destroying the power of the taste glands to perceive bitterness. For this reason it is frequently employed in conjunction with solutions of quinine. The official fluidextract may be given in doses of from one-half to one fluidrachm.

Myrrh.—The gum resin known as myrrh has been employed not only in religious ceremonies but as a remedial agent almost as far back as the beginning of history. It is obtained from the *Commiphora myrrha* and probably allied species of trees found in Arabia and neighboring parts of Africa. The myrrh tree is a bush or small tree, sometimes reaching a height of ten feet.

Myrrh comes into the market in irregular masses or lumps of a brownish color, with a peculiar balsamic odor and a bitter, aromatic taste.

Myrrh possesses the general properties of balsamic oleoresins, and was formerly used as a stimulating expectorant in various types of chronic bronchitis and as a gastric stimulant in chronic dyspepsia. It was believed to be especially stimulating to the uterus, and was at one time considerably employed in the treatment of amenorrhœa. It is still used as a stimulant application to inflamed mucous membranes, especially in chronic gingivitis and aphthous ulcers of the mouth. It enters into the composition of *mistura ferri composita,* which at one time enjoyed a considerable reputation as a hæmatinic, under the name of Griffith's mixture, and also in various cathartic mixtures.

Picrotoxin.—This principle is obtained from the fruit of *Anamirta paniculata,* commonly known as fish berries (*Cocculus Indicus*) from

the fact that they have been used in India for the purpose of stupefying fishes. This principle was at one time recognized by the United States Pharmacopœia and still is official in the British Pharmacopœia. It occurs as colorless crystals insoluble in water at ordinary temperature.

Physiological Action.—Picrotoxin produces violent tonic convulsions later becoming clonic. The convulsions occur in series, being interrupted by periods of muscular quietude. The other symptoms seen in picrotoxin poisoning are salivation, often vomiting, slowing of the pulse; there is often more or less mental confusion and consciousness is generally lost during the convulsion.

In the frog the convulsions persist after destruction of the cerebrum but are greatly lessened or even completely abolished by destroying the medulla oblongata. Some have interpreted this to indicate a stimulant action upon some special convulsive center in the medulla; but the existence of such a center can scarcely be considered established. Although the fact that section of the spinal cord abolishes the convulsions demonstrates that they are not due to spinal stimulation, that the cord is affected is shown by increased reflexes which persist even below the point of section.

Picrotoxin appears to be a stimulant to the whole central nervous system, including the brain, the medulla, and spinal cord. Its action upon the brain is not clearly understood, but that it has some effect upon this organ is shown by the experiments of Koppen, who found that it overcame the sleep caused by chloral.

In the medulla it affects the vasomotor, cardio-inhibitory, respiratory, and probably vomiting centers. It also has some action upon the heat-regulating mechanism, for there is excessive loss of caloric and fall of body temperature under its influence despite the fact that the blood-pressure is increased.

Picrotoxin has been used in medicine as a local agent for the destruction of pediculi but is too dangerous for common employment. Internally it has been given in doses of from $^1/_{100}$ to $^1/_{30}$ grain (0.6 to 2 Mgm.) for the treatment of night-sweats but is of very doubtful utility.

PICROTOXIN.

Grünwald ..... A.E.P.P., 1909, lx, 249.
Hayashi ..... A.E.P.P., 1903, l, 247.
Koppen ..... A.E.P.P., 1892, xxix, 327.

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